SURGERY

VOL. 42 NOVEMBER, 1957 NO. 5

Original Communications

A CLINICAL STUDY OF CHRONIC NONINFECTIOUS THYROIDITIS AND AUTOIMMUNIZATION

JOHN R. PAINE, M.D., KORNEL TERPLAN, M.D., NOEL R. ROSE, PH.D., ERNEST WITEBSKY, M.D., AND RICHARD W. EGAN, M.D., BUFFALO, N. Y.

(From the Departments of Surgery, Pathology, and Bacteriology and Immunology, The University of Buffalo School of Medicine, and The Buffalo General Hospital)

INTRODUCTION

IN PREVIOUS communications, we have reported that the intradermal injection of a saline extract of thyroid tissue of the same species combined with Freund adjuvants produced in rabbits, guinea pigs, and dogs circulating antibodies against the extract used.[9, 10, 12, 14] It is presumed that the protein responsible for this reaction is thyroglobulin. Such antibodies were produced even when the antigen employed was an extract of the thyroid tissue of the experimental animal itself. Circulating antibodies which must be considered true autoantibodies were demonstrated in a large percentage of the experimental animals when the antisera were tested with a homologous saline thyroid extract by means of the tanned cell hemagglutination technique.

The histologic changes in the thyroid glands of the experimental animals following immunization with thyroglobulin or saline extract of thyroid tissue resembled closely the histologic patterns in the thyroid glands of patients with certain types of subacute or chronic thyroiditis.[13] The question then, quite naturally, arose: Are the histologic changes observed in this inflammatory process of so-called chronic thyroiditis due to autoimmunization of the patient with his own thyroglobulin which normally is confined to the intra-acinar colloid of the thyroid? In another publication,[15] we reported that such antibodies were detected in the sera of 12 patients. While our work was in progress, Roitt,

This study was supported in part by a research grant, C-2357, from the National Cancer Institute of the U. S. Public Health Service, and in part by funds supplied by the late Mr. Edward H. Butler and Mrs. Butler.

Received for publication July 29, 1957.

Doniach, Campbell, and Hudson,[8] in a preliminary communication, reported that they had found a precipitin in the sera of some patients with Hashimoto's disease when tested with human thyroid extract.

This present report is based upon a study of the sera of a larger group of patients. An attempt is made to correlate the presence or absence of circulating antibodies against a saline extract of human thyroid tissue with the clinical symptoms and histologic changes in the thyroid gland.

METHOD OF STUDY

The sera of all the patients in this series have been tested for the presence of antibodies against thyroid extract by both the tanned cell hemagglutination technique[12] and precipitation. In general, the hemagglutination test proved to be more sensitive, providing positive results in at least 3 times as many cases as did the precipitation test. The serologic results referred to in this communication were all obtained by the hemagglutination technique. In some cases, more than one sample of the patient's blood, drawn at different times, was examined to determine the significance and constancy of the findings. Titers indicated in the respective tables were reciprocals of the greatest dilution of serum producing a clearly positive agglutination. Every effort has been made to secure histologic slides of the thyroid tissue removed by excision or needle biopsy. These have been carefully reviewed to insure as much uniformity as possible in the differentiation of the various histopathologic types of thyroiditis which were encountered.

RESULTS

A. Controls.—As previously reported,[15] the sera of 120 patients hospitalized for a variety of conditions, exclusive of any thyroid disease, were examined. None of these sera contained demonstrable antibodies against thyroid extract. The sera of 29 additional patients with pathologic changes in the thyroid other than some type of thyroiditis were examined. Pertinent information concerning these patients is given in Table I. The sera of all these patients were found to be negative for the presence of circulating antibodies except in 3 instances. One of these patients (No. 2, M. P.), after a subtotal thyroidectomy for Graves' disease in 1946, experienced a recurrence of her symptoms in September, 1956. Following preparation with propylthiouracil and iodine, a second subtotal resection of the remaining thyroid tissue was performed in March, 1957. A specimen of her serum taken at the time of operation was found on 2 examinations to have circulating antibodies of low titer (27). A second patient (No. 5, P. B.) had a malignant adenoma which developed in the thyroid tissue remaining after a subtotal thyroidectomy for a nodular colloid goiter several years previously. In April, 1957, the malignant adenoma was excised. Samples of serum obtained at the time of operation and a month later were examined. Circulating antibodies were found in both samples, with a titer of 27 in the first one and with a significant increase to 700 in the second. A third patient

(No. 11, M. B.), who was operated upon for a diffuse colloid goiter, had no detectable circulating antibodies in her serum at the time of operation. Five months later, however, a second serum sample gave an antibody titer of 700.

The possibility exists that the appearance of antibodies in the serum of patients who have been subjected to thyroid surgery is due to the surgical

TABLE I. CONTROLS—PATIENTS WITH THYROID PATHOLOGY OTHER THAN THYROIDITIS

PATIENT	DIAGNOSIS	TYPE AND DATE OF OPERATION	RESULT AND DATE OF SERUM EXAMINATION WITH TITER	
1. A. A.	Postop. Graves' disease, hypothyroidism	Subtotal thyroidectomy (1937)	Neg.	Jan., 1957
2. M. P.	Recurrent Graves' disease	Subtotal thyroidectomy (Mar., 1957)	Pos.: 27	Mar., 1957
3. D. R.	Postop. Graves' disease	Subtotal thyroidectomy (1948)	Neg.	Oct., 1956
4. A. B.	Papillary carcinoma	Subtotal thyroidectomy (1947)	Neg.	Apr., 1957
5. P. B.	Malignant adenoma	Subtotal thyroidectomy (Apr., 1957)	Pos.: 27	Apr., 1957
			Pos.: 700	May, 1957
6. P. F.	Anaplastic carcinoma	Biopsy (Mar., 1957)	Neg.	Apr., 1957
7. P. Lo.	Anaplastic carcinoma	Subtotal thyroidectomy (Jan., 1957)	Neg.	Apr., 1957
8. P. Lor.	Hürthle cell carcinoma	Total thyroidectomy (Oct., (1956)	Neg.	Oct., 1956
9. M. W.	Adenocarcinoma	Left lobectomy (June, 1953)	Neg.	Apr., 1957
10. G. A.	Diffuse colloid goiter	None	Neg.	Mar., 1957
11. M. B.	Diffuse colloid goiter	Subtotal thyroidectomy (Oct., 1956)	Neg.	Oct., 1956
			Pos.: 700	Mar., 1957
12. M. P.	Diffuse colloid goiter	Subtotal thyroidectomy (Nov., 1956)	Neg.	Nov., 1956
			Neg.	Mar., 1957
13. G. B.	Toxic nodular goiter	Subtotal thyroidectomy (Mar., 1957)	Neg.	Mar., 1957
14. M. B.	Nodular goiter	Subtotal thyroidectomy (July, 1953)	Neg.	Dec., 1956
15. R. C.	Nodular goiter	Excision of adenoma (Dec., 1956)	Neg.	Dec., 1956
16. B. E.	Nodular goiter	Excision of adenoma (Mar., 1957)	Neg.	Mar., 1957
17. E. E.	Nodular goiter	Subtotal thyroidectomy (Feb., 1953)	Neg.	Nov., 1956
18. C. F.	Nodular goiter	None	Neg.	Apr., 1957
19. E. M.	Nodular goiter	Subtotal thyroidectomy (Feb., 1957)	Neg.	Jan., 1957
			Neg.	Feb., 1957
20. P. P.	Nodular goiter	Right lobectomy (Oct., 1956)	Neg.	Oct., 1956
			Neg.	Dec., 1956
21. M. R.	Nodular goiter	Subtotal thyroidectomy (Jan., 1954)	Neg.	Nov., 1956
22. R. S.	Nodular goiter	Subtotal thyroidectomy (Mar., 1957)	Neg.	Feb., 1957
23. M. S.	Nodular goiter	Subtotal thyroidectomy (Apr., 1957)	Neg.	Apr., 1957
24. B. T.	Nodular goiter	Excision of adenoma (Dec., 1956)	Neg.	Dec., 1956
25. M. V.	Nodular goiter	Excision of adenoma (Mar., 1957)	Neg.	Feb., 1957
26. R. W.	Nodular goiter	Excision of adenoma (Sept., 1954)	Neg.	Nov., 1956
27. C. W.	Nodular goiter	Right lobectomy (May, 1946)	Neg.	Nov., 1956
28. P. M.	Nodular goiter	None	Neg.	Mar., 1957
29. N. N.	Nodular goiter	None	Neg.	Mar., 1957

trauma. Unchanged colloid, acting as an antigen, might have found its way into the circulating blood. In 2 of these cases (No. 5, P. B., and No. 11, M. B.), hemorrhage in the colloid-containing portions of the gland was clearly demonstrable in the histologic slides. That surgery, however, does not always produce this phenomenon is seen from the results in the repeated examinations of the sera of Patients Nos. 12 (M. P.), 19 (E. M.), and 20 (P. P.). Further studies to determine more clearly this point are being carried out at the present time.

B. Patients Clinically Diagnosed as Having Thyroiditis.—The sera of 20 patients with a clinical diagnosis of thyroiditis were examined. No histologic sections from any of these patients were available. Antibodies reacting with thyroid extract were demonstrated in the sera of 5 patients (25 per cent). Pertinent information about these cases is given in Table II. The correctness of the diagnoses in some of these cases might be questioned inasmuch as there is no microscopic proof of the pathologic changes in the thyroid gland. On the other hand, all of these patients with one exception had at some time tenderness in the region of the thyroid accompanied by other signs of a subacute or chronic inflammatory process. The results of laboratory tests, whenever carried out, such as increased basal metabolic rates, increased erythrocyte sedimentation rates, and decreased I^{131} uptakes tended to confirm the diagnosis of subacute thyroiditis.

TABLE II. PATIENTS WITH CLINICAL DIAGNOSIS OF THYROIDITIS AND WITHOUT HISTOLOGIC STUDY

PATIENT	DURATION OF DISEASE	TREATMENT PRIOR TO SERUM EXAMINATION	ACTIVITY OF PROCESS AT TIME OF SERUM EXAMINATION	RESULTS AND DATE OF SERUM EXAMINATION WITH TITER
1. M. G.	6 mo.	Metacortin-x-ray	+++	Pos.: 900 Mar., 1957
2. C. L.	3 mo.	Desiccated thyroid	++	Pos.: 700 Feb., 1957
3. A. M.	3 mo.	None	+	Pos.: 80 Aug., 1956
4. M. R.	1 mo.	None	+	Pos.: 27 Feb., 1957 27 Apr., 1957
5. M. Ga.	30 mo.	ACTH-cortisone	None	Neg. Nov., 1956
6. M. Gi.	16 mo.	Cortisone	None	Neg. Apr., 1957
7. A. N.	26 mo.	X-ray–hydrocortisone	None	Neg. Mar., 1957
8. E. R.	5 mo.	Cortisone	None	Neg. Feb., 1957
9. J. S.	20 mo.	Metacortisone	None	Neg. Mar., 1957
10. M. W.	1 mo.	Cortisone-prednisone	None	Neg. Jan., 1957
11. M. P.	3 mo.	Cortisone–x-ray	None	Neg. Apr., 1957
12. M. A.	3 wk.	Penicillin	++	Neg. Dec., 1956
13. R. B.	1 mo.	None	+	Neg. Dec., 1956
14. B. B.	5 wk.	None	None	Neg. Mar., 1957
15. R. F.	1 mo.	None	+	Neg. Mar., 1957
16. J. J.	1 wk.	None	++	Neg. Jan., 1957
17. H. W.	9 mo.	None	None	Neg. July, 1956
18. A. V.	81 mo.	X-ray–penicillin	None	Neg. Apr., 1957
19. G. M.	21 mo.	None	None	Neg. Jan., 1957
20. M. B.	?	None	++	Pos.: 5,000 Mar., 1957

The one exception (No. 20, M. B.), whose serum was sent to us by Dr. Skillern of the Cleveland Clinic, was considered by him to be a typical case of

struma lymphomatosa, with very mild local symptoms and with definite signs of hypothyroidism, including a basal metabolic rate of –22 per cent, a gamma globulin determination of 1.29 Gm. per cent, and an abnormal T.S.H. test.

It is worthy of note that 7 patients in this group had been given some type of steroid therapy with remission of their symptoms prior to the examination of their sera. The suppresive effect of steroid therapy on all types of immunologic phenomena is well known and would, if our general thesis is correct, adequately explain why none of these patients had detectable circulating antibodies.

Five other patients in whom no antibodies were found had had symptoms for 5 weeks or less prior to the examination of their sera. These findings suggest that free circulating antibodies may not be demonstrable during the first few weeks of the disease.

Three patients, whose initial symptoms had begun 9 months or more prior to the examination of their sera but were asymptomatic at the time of serologic examination, had no detectable antibodies. How long antibodies persist in the serum following a spontaneous or induced remission of the inflammatory state in chronic or subacute thyroiditis is not as yet known.

Of the 5 patients in whose sera antibodies could be demonstrated, one had an unusually high titer of 5,000. This was the patient previously mentioned (No. 20, M. B.), whose case had been diagnosed clinically as struma lymphomatosa (Hashimoto's disease). The remaining 4 patients in whose sera antibodies were found had titers varying from 27 to 900, and there was a close correlation between the titer of antibodies and the duration and severity of clinical symptoms. These patients had the clinical picture associated with subacute thyroiditis (DeQuervain) or chronic nonspecific thyroiditis. Symptoms had been present for more than one month in all of them.

C. Patients With Thyroiditis Proved Histologically.—Forty patients were studied in whom either in the past or more recently the clinical diagnosis of thyroiditis was established and proved by histologic examination of tissue removed from the thyroid gland. Samples of their sera were taken at the time of operation or biopsy and at various times following operation. A summary of the serologic results obtained in this group of patients is given in Table III.

TABLE III. PATIENTS WITH HISTOLOGICALLY PROVED THYROIDITIS

TYPE OF DISEASE	ANTIBODY DEMONSTRATION		
	POSITIVE	NEGATIVE	TOTAL
1. Subacute thyroiditis (DeQuervain)	2	2	4
2. Struma lymphomatosa (Hashimoto)	0	14	14
3. Struma fibrosa (Riedel)	1	3	4
4. Chronic nonspecific thyroditis	14	4	18
	17	23	40

On the basis of histologic characteristics these patients have been divided into 4 groups which are considered as separate entities. It has been recognized for some time that surgical excision of all or part of the thyroid tissue involved in a subacute or chronic noninfectious inflammatory process usually results in

a rather prompt remission of symptoms with an assumed cessation of the inflammatory process. If this be true, according to our present hypothesis, such an event in some way must break the chain reaction by preventing further unchanged colloid from entering the blood stream with the resulting production of antibodies. From this viewpoint, therefore, it is interesting to examine the results reported above and note the time lapse between the excisional thyroid surgery and the serum examination with respect to antibody detection.

TABLE IV. SUBACUTE THYROIDITIS (DEQUERVAIN) IN 4 PATIENTS

PATIENT	DURATION OF DISEASE PRIOR TO SURGERY	OPERATIVE PROCEDURE	INTERVAL BETWEEN OPERATION AND FIRST SERUM EXAMINATION	RESULTS AND DATE OF SERUM EXAMINATION WITH TITER
1. R. B.	3 mo.	Total thyroidectomy	1 wk.	Pos.: 80 Nov., 1956 Pos.: 80 Dec., 1956
2. M. V.	4 yr.	Right lobectomy	1 wk.	Pos.: 80 Apr., 1957
3. J. B.	2 wk.	Subtotal thyroidectomy	25 mo.	Neg. Oct., 1956
4. C. S.	1 mo.	Subtotal thyroidectomy	3 wk.	Neg. Mar., 1957

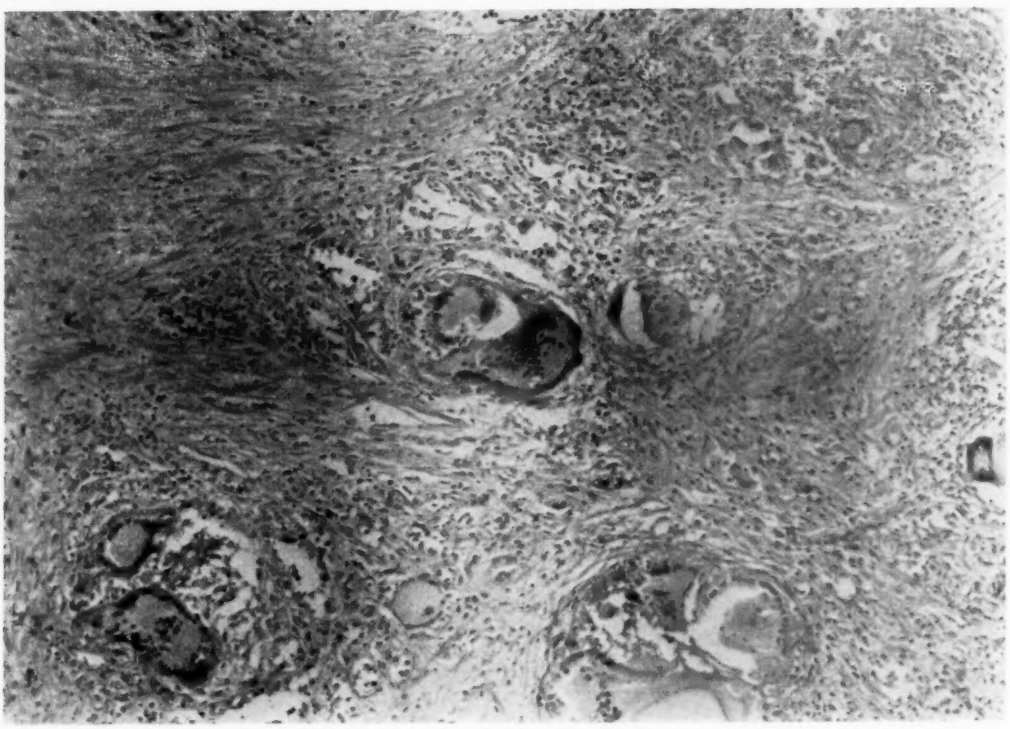


Fig. 1.—Typical picture of DeQuervain type of chronic or subacute thyroiditis. Note the characteristic giant cells in nodular formation surrounding masses of colloid; also, marked fibrosis.

Subacute thyroiditis (DeQuervain) (Table IV and Fig 1): The demonstration of circulating antibodies in the serum of the first 2 patients of this group one week following surgery may be interpreted as indicating that these patients had had thyroiditis for a sufficient length of time prior to operation to

allow the immunizing process to produce a sufficient detectable level of antibodies. On the other hand, in the 2 patients in whom no antibodies were found, symptoms had been present prior to surgery only 2 weeks and one month, respectively. This suggests that such short periods of time are probably insufficient for circulating antibodies to reach a detectable titer. In the instance of Patient No. 3 (J. B.), it is also possible that a remission induced by surgery 25 months prior to the serologic test caused the production of antibodies to cease.

TABLE V. STRUMA FIBROSA (RIEDEL) IN 4 PATIENTS

PATIENT	DURATION OF DISEASE PRIOR TO SURGERY	OPERATIVE PROCEDURE	INTERVAL BETWEEN OPERATION AND SERUM EXAMINATION	RESULTS AND DATE OF SERUM EXAMINATION WITH TITER
1. M. T.	1 yr.	Subtotal thyroidectomy	2 yr.	Pos.: 640 Sept., 1956
2. T. T.	3 mo.	Total thyroidectomy	4 yr.	Neg. Oct., 1956
3. V. H.	1 mo.	Subtotal thyroidectomy	2¼ yr.	Neg. Nov., 1956
4. A. J.	7 mo.	Subtotal thyroidectomy	1¾ yr.	Neg. Mar., 1957

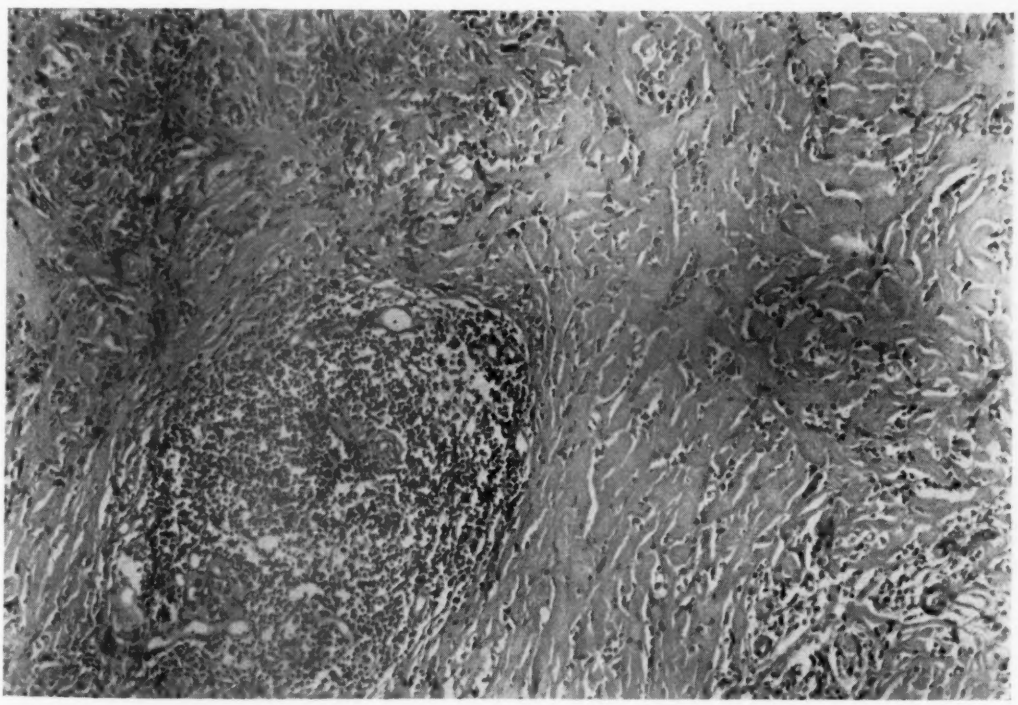


Fig. 2.—Typical picture of fibrous struma (Riedel). Note again the large nodule, consisting mostly of lymphocytes (resembling a lymph follicle), and the extensive hyalinization of the surrounding tissue, with nearly complete obliteration of the original thyroid pattern.

Struma fibrosa (Riedel) (Table V and Fig. 2): One patient in this group had detectable circulating antibodies, and this is rather surprising inasmuch as in this patient subtotal thyroidectomy with relief of symptoms had been performed 2 years prior to the examination of the serum. In the other 3 patients

in whom no antibodies were found, one had symptoms only one month previous to operation. In addition, in all 3, there was a relatively long interval between operation and the examination of their sera. In struma fibrosa, there is little

TABLE VI. STRUMA LYMPHOMATOSA (HASHIMOTO) IN 14 PATIENTS

PATIENT	DURATION OF DISEASE PRIOR TO SURGERY	OPERATIVE PROCEDURE	INTERVAL BETWEEN OPERATION AND FIRST SERUM EXAMINATION	RESULTS AND DATE OF SERUM EXAMINATION WITH TITER
1. R. L.	2 yr.	Needle biopsy	—	Neg. Feb., '57
2. N. S.	1½ yr.	Needle biopsy	—	Neg. Jan., '57
3. C. O'H.	—	Excision nodule	1 wk.	Neg. Mar., '57
4. B. S.	3½ yr.	Total thyroidectomy	4 days	Neg. Jan., '57
5. L. S.	2½ yr.	Subtotal thyroidectomy	1 yr.	Neg. Apr., '57
6. G. R.	11 yr.	Subtotal thyroidectomy	1½ yr.	Neg. June '56
				Neg. Nov., '56
7. G. N.	10 mo.	Subtotal thyroidectomy	7½ mo.	Neg. Jan., '57
				Neg. Apr., '57
8. I. M.	6 wk.	Subtotal thyroidectomy	6 yr.	Neg. Apr., '57
9. F. M.	9 mo.	Subtotal thyroidectomy	1½ yr.	Neg. Apr., '57
10. H. F.	1½ yr.	Subtotal thyroidectomy	1 yr.	Neg. Mar., '57
11. D. D.	4 yr.	Subtotal thyroidectomy	2¾ yr.	Neg. Apr., '57
12. A. C.	2½ yr.	Subtotal thyroidectomy	3 yr.	Neg. Nov., '56
13. B. C.	—	Subtotal thyroidectomy	1 wk.	Neg. Feb., '57
14. V. P.	3 yr.	Subtotal thyroidectomy	1 wk.	Neg. Mar., '57

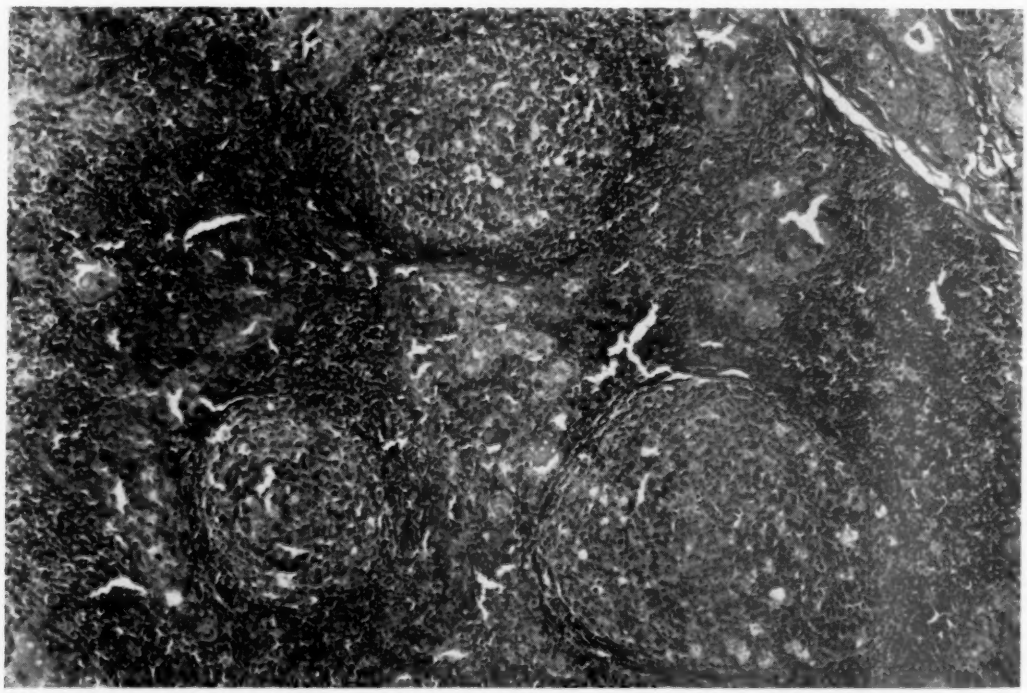


Fig. 3.—Typical lymphadenoid struma (Hashimoto's disease). Note the 3 large lymph follicles and the uniform lymphocytic infiltration in the surrounding parenchyma. There is but little original colloid secretion remaining. (Throughout the tissue removed, the same picture as seen in Fig. 1 is present.)

or sometimes no colloid remaining in the thyroid tissue to furnish antigen. A much greater experience will be required before a reasonable explanation can be offered for the immunologic results observed thus far in this type of lesion.

Struma lymphomatosa (Hashimoto) (Table VI and Fig. 3): Of special interest is the fact that in none of the sera from patients with struma lymphomatosa were antibodies detected. Only those patients who fulfill the strict criteria of Hashimoto's disease, as interpreted by one of us (K. T.), are included in this group. Originally, this group contained 23 patients in whom the initial diagnosis had been that of struma lymphomatosa. These patients were from 6 different hospitals and their histologic sections had been interpreted by 6 different pathologists. In view of the lack of uniformity in what various pathologists believe should be included under the diagnosis of struma lymphomatosa, one of us (K. T.) was asked to review all of the tissue slides of these 23 patients without knowing the results of the serologic examinations except in 4 instances. Nine of these cases were considered to represent a chronic nonspecific thyroiditis instead of Hashimoto's disease. Surprisingly, all 9 of these patients had detectable circulating antibodies against human thyroid extract, but no antibodies were found in any of the remaining 14 patients. It was of particular interest that no antibodies were found in the serum of Patients Nos. 3 (C. O'H.), 4 (B. S.), 13 (B. C.), and 14 (V. P.) inasmuch as the sera of these patients were tested within a few days following operation.

The nature of true Hashimoto's disease is as yet not sufficiently clarified and seems worthy of a great deal more study by immunologic techniques. On the basis of our experience with largely surgical material, our impression is in line with that of Crile[3] that true struma lymphomatosa is relatively rare. The study of our own local material, obtained from various hospitals in Buffalo, has shown that the histologic criteria for the diagnosis of Hashimoto's disease differ. We find ourselves in agreement with the opinions of Statland, Wasserman, and Vickery,[11] regarding the histologic definition of struma lymphomatosa: diffuse dissemination of lymphoid tissue, with lymph follicle formation, parenchymal degeneration, absence of nonlymphocytic infiltration (polymorphonuclear leukocytes, plasma cells, or giant cells). It is for this reason that we are reluctant to use the specific histopathologic term of struma lymphomatosa unless a uniform lymphadenoid transformation of each lobule is present, which in Hashimoto's[5] own words resembles the lymphomatous enlargement of the salivary and lacrimal glands in Mikulicz's disease.

Chronic nonspecific thyroiditis (Table VII and Fig. 4): This group of 18 patients presents a varied picture of histologic changes in the thyroid gland, which, on the basis of our histologic analysis, differs from Hashimoto's disease, Riedel's struma, and from the DeQuervain type of thyroiditis. In some of them, certain features of Hashimoto's disease are present in a few lobules, such as particularly distinct lymph follicles with germinal centers. Other lobules, however, in the same section, are diffusely infiltrated by sheets of plasma cells. The plasma cell in our surgical material, when several or numerous sections were studied, seems to represent the predominating cell type. This is contrary to the original definition of struma lymphomatosa in Hashimoto's[5] description. Also, the degenerative changes of the thyroid epithelium do not show uniformity

in extent and intensity. Fibrosis is quite irregular. It is more or less pronounced in these cases, as is the retention of some of the original, unchanged follicular structure (Fig. 4).

A more specific classification of these cases is impossible unless the criteria of the original descriptions of DeQuervain,[4] Hashimoto,[5] and Riedel[7] are to be so broadened that the original concepts lose their significance. It is remarkable that 14 of the 18 patients in this group had detectable circulating antibodies in their sera—a much higher proportion than in the other groups. More information than is availble at the moment will be required to evaluate properly the 4 patients in this group with negative serum examinations. It is quite

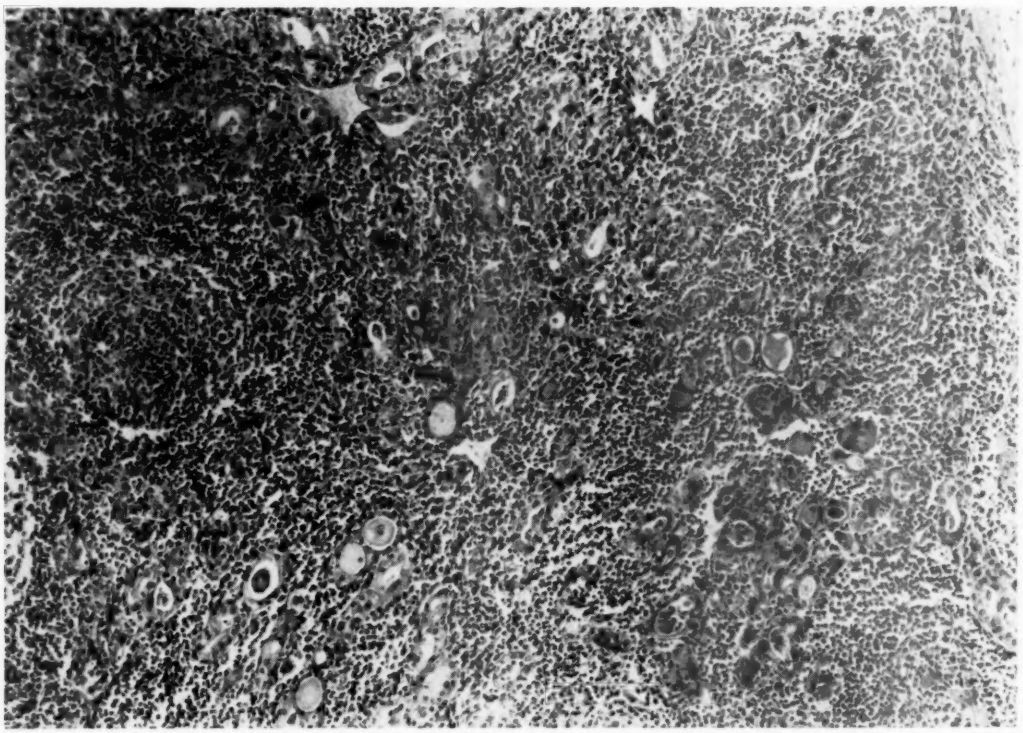


Fig. 4.—Typical area in a case of chronic nonspecific thyroiditis. Note the lymph follicle in the left side of the picture and quite irregular diffuse cellular infiltration (with many plasma cells among them) and a variety of degenerative changes in the thyroid follicles. Some fibrosis in the upper right corner of the picture.

possible that the autoimmunization process must be associated with symptoms for more than one month before sufficient antibodies accumulate to be detected in the serum. The persistence of circulating antibodies in the serum after the subsidence of the inflammatory process in the thyroid, usually occurring after operation, is likewise a matter of speculation at present. We have, however, come to believe that it is unusual to obtain a positive reaction more than 9 months after operation, unless the patient has continued to experience symptoms of inflammation. Attention is drawn to Patient No. 12 (F. R.). This patient is a 30-year-old man who became ill in November, 1954, with pain and soreness in the anterior part of his neck in the region of the thyroid gland.

There was also a mild associated dysphagia. These symptoms persisted without remission until Jan. 3, 1955, when he was operated upon by Dr. H. Kenwell. An excision of the isthmus of the thyroid gland was performed and the diagnosis of thyroiditis confirmed. Following operation, the symptoms persisted until one grain of desiccated thyroid daily was prescribed. This medication controls his symptoms when taken regularly but if omitted for 2 or 3 days, even at the present time, pain and soreness in the region of the thyroid reappear. The antibody titer of 5,000 in this patient's serum is one of the highest that has been found up to the present time.

TABLE VII. CHRONIC NONSPECIFIC THYROIDITIS IN 18 PATIENTS

PATIENT	DURATION OF DISEASE PRIOR TO SURGERY	OPERATIVE PROCEDURE	INTERVAL BETWEEN OPERATION AND FIRST SERUM EXAMINATION	RESULTS AND DATE OF SERUM EXAMINATION WITH TITER
1. J. B.	6 mo.	Subtotal thyroidectomy	1 mo.	Pos.: 240 Nov., 1956
2. M. C.	1 yr.	Total thyroidectomy	4 days	Pos.: 240 Mar., 1957
3. M. D.	2 yr.	Right lobectomy	1 wk.	Pos.: 700 Mar., 1957
4. D. E.	2½ mo.	Right lobectomy	6¾ yr.	Pos.: 2,000 Apr., 1957
5. A. G.	5 yr.	Subtotal thyroidectomy	4 days	Pos.: 9 Feb., 1957 9 Mar., 1957 9 Apr., 1957 9 July, 1957
6. G. H.	9 mo.	Needle biopsy	—	Pos.: 5,000 Nov., 1956
7. J. J.	4 mo.	Needle biopsy	—	Pos.: 2,000 Jan., 1957 2,000 June, 1957
8. K. L.	2 mo.	Subtotal thyroidectomy	5 days	Pos.: 800 Feb., 1957
9. H. M.	1 mo.	Subtotal thyroidectomy	6 yr.	Pos.: 81 Feb., 1957
10. E. M.	2 mo.	Subtotal thyroidectomy	3 mo.	Pos.: 500 Feb., 1957
11. M. R.	6 mo.	Needle biopsy	—	Pos.: 5,000 Feb., 1957 5,000 Apr., 1957
12. F. R.	2 mo.	Excision of isthmus	2¼ yr.	Pos.: 5,000 Apr., 1957
13. M. T.	4 yr.	Right lobectomy	1 day	Pos.: 2,000 Nov., 1956 600 Apr., 1957
14. F. U.	—	Subtotal thyroidectomy	2 yr.	Pos.: 240 Apr., 1957
15. F. A.	3 yr.	Subtotal thyroidectomy	2 yr.	Neg. Oct., 1956
16. E. B.	6 mo.	Subtotal thyroidectomy	5 yr.	Neg. Apr., 1957
17. L. K.	1 mo.	Right lobectomy	2½ yr.	Neg. Nov., 1956
18. M. S.	1 mo.	Right lobectomy	3 days	Neg. Apr., 1957 Neg. May, 1957

DISCUSSION

There would seem to be little doubt that at least in many instances of subacute or chronic noninfectious thyroiditis autoimmunization of the patient against constituents of his own thyroid gland, presumably thyroglobulin, takes place. The mechanism by which the unchanged thyroglobulin of the colloid

gains entrance to the bloodstream to act as a true antigen has not been explained. In 2 instances of chronic nonspecific thyroiditis in our local surgical material, quite incidentally, colloid with a normal staining reaction has been demonstrated within the lumen of capillary veins. Whether or not the resorption of colloid by macrophages invading the acini and its release into the interfollicular stroma as observed by Chesky and associates[1, 2] and Hellwig[5] is already the manifestation of antibodies present or actually a part of the mechanism leading to their formation is not known.

Previous reports by 2 of us (E. W. and N. R. R.),[9, 12] concerning the immunologic aspects of experiemental thyroiditis in animals, combined with the observations here reported, fulfill the criteria which establish certain forms of chronic noninfectious thyroiditis as an autoimmune disease, as previously postulated.[15]

The evidence for this is as follows. (1) Antibodies against thyroid extract circulating in the bloodstream have been demonstrated in patients with thyroiditis. (2) Information available so far points to thyroglobulin as the specific antigen against which these antibodies are directed. (3) Autoantibodies against the same antigen have been produced in 3 species of experimental animals. (4) Pathologic changes in the thyroid glands of the experimental animals which have been actively sensitized resemble those occurring in the thyroid gland of patients with noninfectious thyroiditis.

The sera of most patients representing all the recognized types of nonspecific thyroiditis as proved by histologic study have been found to contain antibodies against thyroid extract. In contrast, no circulating antibodies were found in the serum of those 14 patients considered to have Hashimoto's disease as defined by a strict interpretation of the histologic picture. The failure to demonstrate circulating antibodies in all patients with noninfectious thyroiditis cannot be construed as evidence against the autoimmune nature of this condition. Any of a variety of reasons may explain why any specific patient at any specific time fails to have a sufficiently high level of antibodies in his serum to be demonstrable.

Under the circumstances of autoimmunization in which the patient has a large store of antigen such as the intrafollicular thyroglobulin, the titer of antibodies in the circulating blood will depend upon the balance of antibody production and antibody absorption by the thyroglobulin still remaining in the thyroid gland. It is our concept that this absorption of antibodies with the accompanying antigen-antibody reaction occasions the inflammatory response with the subjective symptoms of thyroiditis. As a result of this reaction, additional quantities of colloid find their way into the bloodstream and a chain reaction type of process is instituted. This may well vary in its severity as the process continues. The duration of the disease must also be taken into account. Some period of time, which without doubt varies from patient to patient, must transpire before antibodies can reach a sufficient level in the bloodstream to be detected after the immunization process has begun. One cannot be sure that

the duration of symptoms coincides with the duration of immunization. Judging from our experience thus far, however, it would seem to be unusual to demonstrate circulating antibodies until symptoms, however severe, have been present for one month or more. In many patients the immunizing process stops either temporarily or permanently. In some instances this occurs spontaneously and in other instances surgical excision seems to produce the same result. The dramatic fashion in which all symptoms of subacute thyroiditis subside, at least in some instances, after instituting steroid therapy, suggests that the immune reactions are rapidly and effectively suppressed. It is also possible that both x-ray treatment and thiouracil-type drugs may terminate the process of autoimmunization. The evidence for this, however, is equivocal. In any event, whatever stops the chain reaction and thereby the production of antibodies, it is not to be expected that antibodies already produced will remain circulating in the serum indefinitely. Indeed, on the basis of our experience up to the present time, it would appear that a positive hemagglutination test is unusual if performed more than 9 months after all clinical symptoms have subsided. In rare instances, however, antibodies have been detected as long as 2 years after remission of the clinical symptoms.

The demonstration of circulating antibodies in patients with all the classically described types of noninfectious thyroiditis with the exception of Hashimoto's struma could be interpreted in favor of the concept that these conditions, in spite of the differences in their histologic patterns, are not necessarily separate and distinct diseases. In the light of our present knowledge it seems more logical to consider thyroiditis as an evolutionary process which, with the passage of time and because of factors not now known, can present itself by a variety of histologic pictures.* Clinical observations indicate, however, that, if such is the case, the time required for the end stage to be reached is subject to considerable variation, and the degree of histologic change is not necessarily correlated with the severity of clinical symptoms.

The nature of Hashimoto's disease, in contrast to other types of chronic thyroiditis, has not been sufficiently clarified in relation to autoimmune mechanisms. As noted above, when the diagnosis is based on strict interpretation of histologic changes, affecting the gland uniformly, no antibodies have been detected so far. Whether or not true Hashimoto's disease is an entity, entirely different from the other types of chronic thyroiditis, without any links to immunologic phenomena, or is a phase of chronic thyroiditis in which immunization has ceased, we do not know. Cases of chronic nonspecific thyroiditis which do not fulfill the strict criteria of Hashimoto's disease but in which antibodies of a high titer have frequently been demonstrated could represent earlier stages of the evolutionary process during which immunization is still active. Much additional research will have to be done before the answers to this problem are known.

*This interesting concept was first presented by T. Levitt: Status of Lymphadenoid Goitre, Hashimoto's and Riedel's Diseases; Hunterian Lecture, Ann. Roy. Coll. Surgeons England **10**: 369, 1952.

Despite some current opinions concerning the likelihood of other human diseases being a manifestation of autoimmune processes, proof in any instance has been equivocal up to the present time. Such proof is now available in certain cases of chronic or subacute noninfectious thyroiditis. The concept of autoimmunization as the possible cause of a disease must therefore be accepted. Other diseases of unknown etiology should, therefore, be reappraised and studied anew from this viewpoint.

SUMMARY

The sera of a relatively large number of patients with and without thyroiditis have been tested for the presence of circulating antibodies against thyroid extract by the tanned cell hemagglutination technique as well as by precipitation. Due to the greater sensitivity of the hemagglutination test, all reported results are based upon that method of examination.

In the control group of patients, results were as follows.

1. In 120 patients hospitalized for a variety of conditions exclusive of thyroid diseases, no thyroid antibodies could be demonstrated.

2. Among 29 patients with pathology of the thyroid other than some type of thyroiditis, antibodies were found in 3. The sera of these 3 patients were all obtained following operation for the following conditions: (a) recurrent exophthalmic goiter, (b) malignant adenoma, and (c) diffuse colloid goiter.

Circulating antibodies were demonstrated in the sera of 5 out of 20 patients diagnosed clinically as some type of noninfectious thyroiditis but without histologic examination. Four of these patients had the symptoms of the subacute or chronic nonspecific type of disease and one had the clinical picture usually associated with Hashimoto's disease.

3. Forty patients in whom sections of the thyroid were available for examination were classified in 4 groups on the basis of histologic study as follows: (a) subacute thyroiditis (DeQuervain), 4; (b) struma fibrosa (Riedel), 4; (c) struma lymphomatosa (Hashimoto), 14; (d) chronic nonspecific thyroiditis, 18.

Circulating antibodies were demonstrated in some of the patients comprising each of these groups except in those patients considered to have struma lymphomatosa. In this latter group, no antibodies could be demonstrated in any of the 14 patients. The greatest number of positive reactions occurred in the chronic nonspecific thyroiditis group.

CONCLUSIONS

1. Patients with chronic noninfectious thyroiditis, usually classified under the headings (a) subacute thyroiditis (DeQuervain), (b) struma fibrosa (Riedel), and (c) chronic nonspecific thyroiditis, are examples of autoimmunization by some constituent of their own thyroid tissue. This substance is probably thyroglobulin.

2. Circulating antibodies in the sera of patients with thyroiditis were demonstrated during the active phase of the disease in most instances.

3. A period of 4 weeks or more after the onset of symptoms seems to be required for circulating antibodies to reach a sufficient level to be detected by the hemagglutination technique.

4. After remission of clinical symptoms occurring spontaneously or induced by drugs or surgery it is unusual to detect circulating antibodies after a period of 9 months or more has elapsed.

5. No evidence has been found so far to associate struma lymphomatosa (Hashimoto) as defined by a strict interpretation of the histologic picture with an autoimmune process.

6. Other diseases of unknown etiology should be reconsidered from the standpoint of certain criteria laid down by us in a previous communication as possibly being caused by an autoimmune process.

REFERENCES

1. Chesky, V. E., Dreese, W. C., and Hellwig, C. A.: Chronic Thyroiditis: Supravital Studies of Surgical Goiter Specimens, Surg., Gynec. & Obst. **93**: 575, 1951.
2. Chesky, V. E., Dreese, W. C., and Hellwig, C. A.: Chronic Thyroiditis: Review of Forty-Two Cases, J. Internat. Coll. Surgeons **21**: 679, 1954.
3. Crile, G., Jr.: Thyroiditis, Ann. Surg. **127**: 640, 1948.
4. DeQuervain, F.: Die akute, nicht eiterige Thyroiditis und die Beteiligung der Schilddrüse an akuten Intoxikationen und Infektionen überhaupt, Mitt Grenzgeb. Med. u. Chir., Supp. 2, p. 1, 1904.
5. Hashimoto, H.: Zur Kenntniss der lymphomatösen Veränderung der Schilddrüse (Struma lymphomatosa), Arch. klin. Chir. **97**: 219, 1912.
6. Hellwig, C. A., and Wilkinson, P. N.: Experimental Production of Thyroiditis, A. M. A. Arch. Path. **62**: 23, 1956.
7. Riedel, B.: Die Chronische zur Bildung eisenharter Tumoren führende Entzündung der Schilddrüse, Verhandl. deutsch. Gesellsch. Chir. **25**: 101, 1896.
8. Roitt, I. M., Donich, D., Campbell, P. N., and Hudson, R. V.: Auto-antibodies in Hashimoto's Disease (Lymphadenoid Goitre), Lancet **2**: 820, 1956.
9. Rose, N. R., and Witebsky, E.: Studies on Organ Specificity. V. Changes in the Thyroid Glands of Rabbits Following Active Immunization With Rabbit Thyroid Extracts, J. Immunol. **76**: 417, 1956.
10. Rose, N. R., and Witebsky, E.: Production of Specific Rabbit Thyroid Antibodies in the Rabbit, Fed. Proc. **15**: 609, 1956.
11. Statland, H., Wasserman, M. M., and Vickery, A. L.: Struma Lymphomatosa (Hashimoto's Struma), Arch. Int. Med. **88**: 659, 1951.
12. Witebsky, E., and Rose, N. R.: Studies on Organ Specificity. IV. Production of Rabbit Thyroid Antibodies in the Rabbit, J. Immunol. **76**: 408, 1956.
13. Witebsky, E., Rose, N. R., Paine, J. R., and Egan, R. W.: Thyroid-Specific Antibodies, Ann. New York Acad. Sc. In press.
14. Witebsky, E., Rose, N. R., and Shulman, S.: Studies of Normal and Malignant Tissue Antigens, Cancer Research **16**: 831, 1956.
15. Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, R. W.: Chronic Thyroiditis and Auto-Immunization, J. A. M. A. **164**: 1439, 1957.

ALTERATIONS IN THYROID FUNCTION FOLLOWING SURGICAL TRAUMA

ARTHUR E. SCHWARTZ, M.D., AND KATHLEEN E. ROBERTS, M.D., NEW YORK, N. Y.

(From the Departments of Surgery and Medicine, Memorial Center, and the Andre and Bella Meyer Physiology Laboratories, Sloan-Kettering Institute)

INTRODUCTION

SURGICAL trauma produces pituitary, adrenocortical, thyroid, and electrolyte response patterns which have yet to be fully elucidated. Investigators using protein-bound iodine (PBI) and butanol extractable iodide serum levels as a measure of thyroid activity have found no significant alterations during the postoperative period at varying intervals of 12, 24, and 48 hours.[4, 6] Peters and Man[8] conclude, "Stress or surgery produces a fall in the level of PBI of 0.5 to 3.0 mg. per cent within the first day or two, and a return to normal over a variable interval, the degree and rate of fall being roughly proportional to the severity of the trauma." The present study was undertaken to determine whether there might be an immediate thyroid response in the first few hours following surgery which could have been overlooked by investigators employing PBI determinations at 12-, 24-, and 48-hour intervals. Because of earlier work in our laboratory demonstrating that infused phosphate potentiates the action of tri-iodothyronine (T-3) in dogs,[9] serum determinations of phosphorus, calcium, and magnesium in the postoperative state were also studied.

METHODS AND MATERIALS

In the course of the investigation 21 patients undergoing major surgery were studied. These included procedures in the immediate area of the thyroid gland, such as radical neck dissections, as well as those remote from the neck. In the first 8 cases control values were obtained before surgery, and following operation samples were drawn at 2-hour intervals for 10 hours. These were compared to values 24 hours postoperatively. It became apparent during these initial studies that the changes in PBI occurred within the first 2 hours after surgery, and accordingly the specimens were obtained from the remaining patients as soon after surgery as practicable (that is, within 3 hours of the completion of surgery). In 8 patients concomitant hematocrits were drawn to determine whether hemodilution or concentration factors were distorting PBI or electrolyte levels. Plasma calcium, potassium, and magnesium concentrations were studied in all specimens.

Protein-bound iodine was determined by the Zak method[10] as modified by Bodansky,[2] calcium by the method of Clark and Collip,[3] inorganic phosphates by the method of Fiske and Subbarow,[5] and magnesium by Heagy.[7]

Received for publication March 12, 1957.

RESULTS

In every patient except one (J. C.) there was an elevation of the PBI during the first few hours following surgery. The general pattern was an initial sharp rise over the control level during the first 3 hours after surgery, then a gradual decline, usually to values below the control, in 24 hours (Fig. 1 and Table I).

It was of interest that the elevations in patients who had procedures involving manipulation of the thyroid gland itself were of the same order as in those undergoing procedures in areas remote from the gland, which suggests a true hormonal rather than a mechanical response (Table I).

Because all the surgery studied was of a major nature we were unable to draw any conclusion regarding the relationship of the severity of the trauma to the extent of the rise in PBI. However, a definite and consistent rise in the level of circulating thyroid hormone following surgery was observed. This usually declined below preoperative levels by 24 hours, suggesting a possible suppression or increased utilization of thyroid hormone at this period.

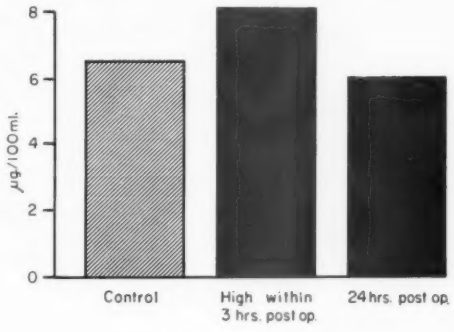


Fig. 1.

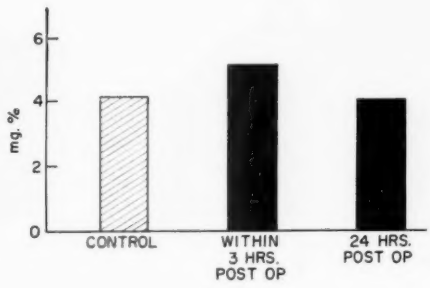


Fig. 2.

Fig. 1.—Changes in protein-bound iodine (PBI) in postoperative patients (average of 18 patients).

Fig. 2.—Changes in phosphorus in postoperative patients (average of 21 patients).

Phosphorus.—The serum phosphorus levels in 14 patients showed a marked increase within the first 2 to 3 hours following surgery and usually returned toward control levels by 24 hours. In 7 patients there was either no change or only a slight decrease in serum phosphorus levels. It seems significant that when the serum phosphorus did rise it often increased markedly, up to 50 to 75 per cent. There was no particular correlation between the phosphorus elevation and PBI. The average elevation in 21 patients was 0.8 mg. per cent as shown in Fig. 2. In 7 patients who showed no change or whose phosphorus level went down the average control was 4.6, and the postoperative average was 4.3. In the 14 patients whose phosphorus level rose the control average was 4.1 and the postoperative average was 5.5.

Calcium.—In general, the calcium levels declined within the first few hours following surgery and were often at significantly lower levels at the 24-hour period. There were a few patients, however, who did not show a drop in calcium and, indeed, showed elevated values.

TABLE I. CHANGES IN PLASMA CONCENTRATION OF PROTEIN-BOUND IODINE (PBI), CALCIUM, MAGNESIUM, AND PHOSPHATE IN POSTOPERATIVE PATIENTS

PATIENT AND OPERATION	PBI (MG. %)			PHOSPHORUS (MG. %)			CALCIUM (MG. %)			MAGNESIUM (MG. %)		
	CONTROL	WITHIN 3 HOURS	24 HOURS	CONTROL	WITHIN 3 HOURS	24 HOURS	CONTROL	WITHIN 3 HOURS	24 HOURS	CONTROL	WITHIN 3 HOURS	24 HOURS
W. G. (radical neck bilateral and total laryngectomy)	5.6	6.8	4.6	3.5	4.2	3.4	9.4	8.5	8.4	2.3	2.0	2.3
L. K. (radical pneumonectomy)	7.0	7.6	5.2	4.8	7.4	3.8	8.8	8.0	7.8	2.5	2.3	2.6
E. H. (radical breast)	7.2	8.8	5.5	6.0	5.7	5.4	10.0	8.4	9.9	2.8	2.4	2.5
R. S. (radical breast)	6.1	8.7	6.7	5.4	5.1	4.5	9.7	8.2	7.6	2.8	2.0	2.3
C. S. (radical neck)	7.8	7.9	5.6	4.8	7.4	4.5	9.6	9.3	9.7	1.4	1.3	1.5
J. V. (radical neck)	7.1	10.6	7.1	4.8	5.1	5.3	--	--	--	2.7	1.7	2.5
M. L. (intestinal resection)	4.6	4.9	4.8	3.2	5.1	5.9	11.2	9.7	9.9	2.1	1.8	1.7
E. A. (radical neck)	6.2	7.1	6.8	4.5	4.5	4.0	10.7	10.6	10.5	2.2	1.9	2.3
J. P. (larynx and neck)	4.0	7.3	3.2	3.8	4.5	2.4	11.2	10.2	9.8	2.6	1.9	2.3
J. C. (rectal "pull through")	10.5	10.3	8.8	3.8	3.8	2.2	11.2	10.2	10.2	2.3	1.9	2.0
A. D. (subtotal gastrectomy)	5.8	9.1	6.7	4.2	4.5	4.8	10.9	10.8	10.5	2.4	2.0	2.3
J. K. (radical breast)	7.4	9.1	--	3.6	6.2	2.6	10.7	10.2	10.8	2.0	2.1	1.7
A. W. (bilateral adrenalectomy)	6.0	8.7	5.2	4.2	3.6	3.2	10.2	10.2	10.2	--	--	--
A. N. (orbital and maxillary exenteration)	7.5	8.1	5.4	4.4	5.8	4.0	10.7	10.8	10.4	2.1	2.2	2.2
L. F. (bilateral adrenalectomy)	6.1	8.7	5.7	4.0	4.0	4.5	11.3	10.6	11.6	2.4	1.9	1.6
A. N. (exploratory thoracotomy)	4.6	6.5	8.7	4.9	5.8	5.2	11.2	10.7	11.2	2.3	2.1	2.3
J. S. (orbital and maxillary exenteration)	7.1	8.4	6.9	4.0	5.4	4.8	11.5	10.4	12.2	2.7	2.4	2.3
O. H. (radical pneumonectomy)	6.2	7.1	3.4	4.0	5.4	3.0	10.3	9.9	10.0	2.1	1.9	2.4
F. G. (subtotal gastrectomy)				3.5	3.8	3.4	9.4	8.5	8.4	2.3	2.0	2.3
H. C. (hysterectomy and node resection)				4.3	3.4	3.0 (12 hr.)	9.2	8.9	8.3	2.2	1.9	2.4
A. P. (radical pneumonectomy)				4.4	7.0	3.4	10.4	10.3	10.2	--	--	--
Average	6.5	8.1	6.0	4.3	5.1	4.0	10.4	9.7	9.9	2.3	2.0	2.2

Magnesium.—Magnesium levels consistently showed a slight decrease immediately after surgery which usually returned to about normal values in 10 hours. The significance of this is not known but it is consistent with the observation that in dogs given T-3 and then infused with phosphates the magnesium levels drop.

Hematocrit.—In the 8 patients whose hematocrit was studied there were no significant changes which would affect our values. Indeed, the hematocrit was usually unchanged or slightly higher in the immediate postoperative interval during which they were studied.

DISCUSSION

Work in which radioactive iodine uptake has been used as a measure of thyroid activity and urinary excretion of corticosteroids has suggested a functional antagonism between the thyroid and adrenal cortex in the postoperative state.[6] Goldenberg and associates[6] found varying patterns of response which could be grouped as follows: (a) increased thyroid activity immediately after surgery, followed by increased adrenocortical activity which was, in turn, followed by suppression of thyroid function; (b) increased adrenocortical activity with depressed thyroid activity immediately postoperatively; (c) increased thyroid activity with unchanged adrenocortical activity; and (d) no significant change in thyroid or adrenocortical response.

Our work suggests that there is a consistent rise in the level of circulating thyroid hormone in the first 3 hours after surgical trauma and that by 24 hours there is a depression of circulating thyroid hormone to below preoperative levels. Roberts and co-workers[9] have demonstrated that infusion of sodium phosphate potentiates the action of tri-iodothyronine in dogs, producing an increased oxygen consumption, tachypnea, and cardiovascular collapse resembling thyroid crisis. These changes were not observed when either T-3 or phosphate alone were infused. It is possible that the marked increase in phosphate levels in some of our postoperative patients could potentiate the action of the increased levels of circulating thyroid hormone.

The tachycardia observed after giving thyroxine to rabbits has been found to continue for several hours, even after the heart has been excised and transferred to a Ringer-Locke solution.[1] The tachycardia which follows surgery and usually resolves spontaneously could be related to the transient increased hormone level after surgery. Most of the patients studied demonstrated an increased pulse rate postoperatively, ranging from 10 to 20, although it was not correlated quantitatively with the elevations in PBI. This increased level of thyroid hormone potentiated by significant increases in plasma phosphate levels may be a factor in the thyroid storm so often seen in earlier days following thyroidectomy, but often following other surgery as well.

SUMMARY

There was a definite and consistent rise in PBI within 3 hours after surgery which usually fell to below control levels by 24 hours.

Immediately after surgery there was a marked rise in serum phosphate levels in most patients (14) with little change or slight decrease in the remaining 7 patients.

Plasma magnesium concentration usually decreased slightly and returned to normal values in about 10 hours.

The plasma calcium concentration, in most cases, fell immediately following surgery and remained at these lower levels for 24 hours.

REFERENCES

1. Blades, Brian: Nash's Surgical Physiology, Springfield, Ill., 1953, Charles C Thomas, Publisher, p. 508.
2. Bodansky, O.: Personal communication; Modification of Zak Method, to be published.
3. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium With a Suggested Modification, J. Biol. Chem. **63**: 461, 1925.
4. Engstrom, W. W., and Markardt, B.: Serum Precipitable Iodine in Surgical Stress and Serious Illness, J. Clin. Invest. **33**: 931, 1954.
5. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**: 375, 1925.
6. Goldenberg, I. S., Rosenbaum, P. J., and Hayes, M. A.: Patterns of Thyroid-Adrenocortical Response After Operation, Ann. Surg. **142**: 786, 1955.
7. Heagy, F. C.: The Use of Polyvinyl Alcohol in the Colorimetric Determination of Magnesium in Plasma or Serum by Means of Titan Yellow, Canad. J. Research **26E**: 295, 1948.
8. Peters, J. P., and Man, E.: The Thyroid, Werner, 1955, Paul B. Hoeber, Inc., p. 144.
9. Roberts, K. E., Firmat, G., Prunier, J., Schwartz, M. K., and Rawson, R. W.: Effect of Phosphate in Enhancing the Action of Tri-iodothyronine, Endocrinology **59**: 565, 1956.
10. Zak, B., Willard, N. H., Myers, G. B., and Boyle, A. T.: Chloric Acid Method for Protein Bound Iodine, Analytical Chem. **24**: 1345, 1952.

RANULAS WITH EXTENSION INTO THE NECK (SO-CALLED PLUNGING RANULAS)

GEORGE CRILE, JR., M.D., CLEVELAND, OHIO

(From the Department of General Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute)

A RANULA, by definition, is "a cystic tumor beneath the tongue, due to obstruction and dilatation of the sublingual or submaxillary gland or of a mucous gland." When the cystic cavity of a ranula over a period of years gravitates downward into the neck, it may present in midneck or even low in the neck as a soft, cystic mass filled with mucus. Repeated excisions of the cyst itself may fail to control the ranula unless the mucous gland which caused it is also excised. Two cases illustrating this unusal condition are herewith reported.

CASE REPORTS

CASE 1.—The patient was a woman 36 years of age, who developed a cyst in the right side of her neck in July, 1949. Treatment at another hospital consisted of 4 operations. First the cyst was drained externally, then marsupialized, then packed with iodoform gauze, and then the neck was explored with the hope of resecting the lesion which extended from the base of the skull to the jugular notch. Roentgen therapy (1800 r) also was given without improvement.

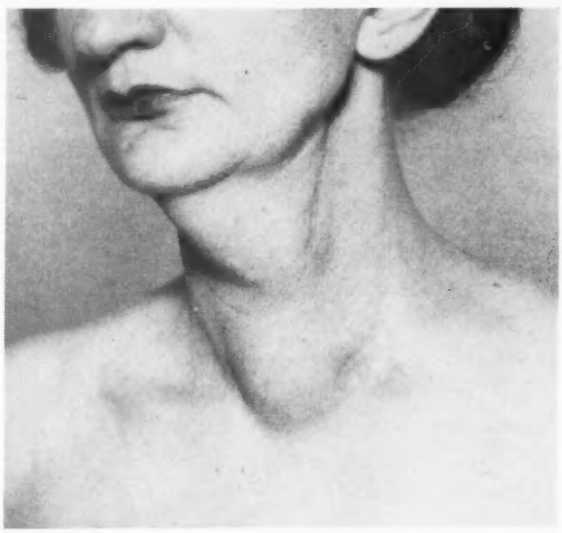


Fig. 1.—Case 1. Plunging ranula. The mucus-filled cyst extends from the submaxillary region to the clavicle.

In 1951, the patient still had a huge cyst which filled the right side of the neck (Fig. 1). It was soft, fluctuant, and on aspiration was found to be filled with clear mucus

Received for publication Jan. 29, 1957.

which was thick and stringy. The soft swelling was palpable on the floor of the mouth as well as in the neck. Further questioning of the patient showed that at the age of 9 she had had an intraoral operation for what sounded like a ranula.

In June, 1951, a transverse cervical incision was made over the cyst, and skin flaps were raised by sharp dissection. The sac was carefully separated from the underlying facia and muscles and finally was mobilized intact, except where it was adherent to the floor of the mouth. At this point the mouth was entered and some mucous membrane of the floor of the mouth was resected with the cyst. The sublingual gland likewise was resected and appeared to be in continuity with the cystic structure.

The pathologist reported that the cyst wall was fibrous, with no epithelial lining and with foreign-body reaction in the tissue of the lining surface.

Five years after operation, the patient was well and had had no recurrence of the cyst.

CASE 2.—The patient was a woman 30 years of age, who for the past 18 years had had a cyst in the left side of the neck under the mandible. At times it had become as large as an orange, and she had had 4 major operations with resection of the cyst and several others in which the cyst had been incised and drained.

Examination showed a soft, fluctuant swelling in the upper neck on the left which was also palpable in the floor of the mouth. Aspiration of the cyst showed thick, stringy mucus.

In July, 1955, the cystic mass was excised intact, but no connection with salivary glands was noted. The pathologist reported a fibrotic cyst with lipophage infiltration and foreign-body reaction. There was no epithelial lining.

A few weeks after operation, the cyst recurred. A second operation was done through a transverse submental incision and the cyst was re-excised. Dissection was carried up to the floor of the mouth where the cyst appeared to be adherent to a glandular structure. It was thought that this was a sublingual salivary gland, and it was excised with the cyst. The pathologist, as before, described no evidence of an epithelial lining in the cyst but mentioned the mucous gland fragments which were removed from the sublingual area. Healing was prompt and complete, and 9 months later there was no further recurrence of the cyst.

COMMENT

Cysts of the sublingual salivary gland usually present themselves as swellings in the floor of the mouth called ranulas, but it appears that under certain circumstances these cysts may dissect downward into the neck and cause huge mucus-filled cysts which may dissect down as low as the clavicle. Twenty-five such cases occurring in the South African Bantus have been reported by Keen, Cohen, and Shapiro[2] who treated the cysts successfully by injecting bismuth oxychloride and giving x-ray therapy. In the older literature several cases were mentioned in 1927 by Fitzwilliams[1] who made an extensive summary of the literature on the subject and concluded that the plunging ranulas arose in the salivary glands and worked their way downward in the neck. These cysts do not have epithelial linings and perhaps they could be obliterated simply by excision of the salivary gland from which the mucous secretion comes.

In neither of the cases reported here was the operation done by simply removing the salivary gland. In the first case the entire cyst was removed. In the second, although the cyst ruptured in the course of removal, most of the cyst was removed as well as the gland which caused it. In the future, in dealing with very large cysts, it might be wise to try converting the cyst to a

draining sinus by inserting a mushroom catheter to drain it and then at a secondary operation the sinus could be followed up to the salivary gland and the gland excised. In any event it seems certain that simple excision of the fibrous wall of the cyst without removal of the gland is doomed to failure.

SUMMARY

Two cases of ranulas extending into the neck and recurring after multiple excisions of the mucus-filled cysts are reported. Cure was effected by removing the sublingual salivary gland from which the mucus originated.

REFERENCES

1. Fitzwilliams, D. C. L.: The Tongue and Its Diseases, New York, 1927, Oxford University Press.
2. Keen, P., Cohen, L., and Shapiro, M. P.: Plunging Ranula: New Therapeutic Approach (Photoelectron Radiation From Roentgenotherapy After Introduction of Bismuth), South African M. J. **28**: 189, 1954.

THE COAGULATION DEFECT AFTER HEPATECTOMY

WORTHINGTON G. SCHENK, JR., M.D., JOHN FOPEANO, PH.D., JAMES H. COSGRIFF, JR., M.D., AND JAMES G. GRAY, M.D., BUFFALO, N. Y.

(From the Department of Surgery, University of Buffalo, School of Medicine, and the Edward J. Meyer Memorial Hospital)

A TIME-HONORED method for study of single organ function has been removal of that organ followed by study of the physiologic defect produced by its absence. This general method of study applies to the liver as well as many other organs but has been used by relatively few investigators. Preparation of a liverless animal which is otherwise in good condition is a major surgical challenge and this obstacle has probably discouraged many investigators. Relatively few contributions have been made to the subject since the monumental work of Mann and his associates over 30 years ago. They showed that the liverless dog dies in 4 to 8 hours in hypoglycemic shock unless supported by glucose infusions.[4] When supported with glucose infusions sufficient to maintain the blood sugar at normal or elevated levels the animals lived longer, yet uniformly succumbed in 18 to 24 hours. The cause of death in such animals has never been satisfactorily elucidated.

Mann[3] observed a typical clinical picture preceding death in these animals which included progressive tachycardia and hypotension. Markowitz[5] notes that these animals uniformly have significant quantities of free blood in the peritoneal cavity at autopsy. We have undertaken the preparation of 68 liverless dogs in the past year in an effort to clarify the mechanism of death in such animals. A portion of the findings is reported here.

METHOD

Hepatectomy was performed by the two-stage method of Markowitz and Soskin[6] modified only in that the gastrohepatic omentum was divided at the first stage to prevent venous collateral formation in that structure. Whole blood was administered if necessary during the second stage to replace that which was lost. Penicillin G, crystalline, was administered to minimize the possibility of infection influencing the outcome. Blood pressure was observed continuously using a mercury manometer attached to an arterial catheter.

RESULTS

Eight dogs were supported after hepatectomy by a continuous infusion of 7.5 per cent glucose in one third normal saline administered at a rate of 0.5 Gm. glucose per kilogram of body weight per hour. The course in these dogs

Supported in part by a Grant-in-Aid from the Heart Institute, United States Public Health Service.

Received for publication Jan. 24, 1957.

was rather uniform and identical to that previously described. For approximately 12 hours the animals looked clinically well. They were awake and alert, would eat or drink, and had normal pulse and blood pressure values. From that point on, progressive deterioration occurred with tachycardia, hypotension, coma, and death in 17 to 20 hours. In most animals, bleeding from the wound became evident in the 2 to 3 hours preceding death although no bleeding had been noted prior to that time. At autopsy all animals were found to have large quantities of liquid blood in the peritoneal cavity usually representing 20 to 30 per cent of the animal's blood volume. In addition, in some animals extensive ecchymotic areas were found remote from the operative site, particularly in the superior mediastinum, parietal pleura, and serosal surfaces of bowel.

Since this extensive blood loss did not appear to be the result of technical error, the coagulation determinations were carried out as shown in Tables I and II. Prothrombin time was determined by the one-stage method of Quick. It will be seen that both clotting time and prothrombin time became infinite terminally.

TABLE I. PROTHROMBIN TIME AFTER HEPATECTOMY
(Animal Supported with Glucose Only)

DOG NUMBER	PROTHROMBIN TIME (SECONDS)		SURVIVAL TIME (HOURS)
	IMMEDIATE POSTOPERATIVE	TERMINAL	
5165	10.4	No clot	17½
5265	10.0	No clot	17
675	9.6	No clot	17¾
6135	10.0	No clot	17

TABLE II. COAGULATION TIME AFTER HEPATECTOMY
(Animal Supported With Glucose Only)

DOG NUMBER	COAGULATION TIME (MINUTES)		SURVIVAL TIME (HOURS)
	PREOPERATIVE	TERMINAL	
12275	3	No clot	19
226	4	No clot	19¼
3126	4	Over 20; watery	19½
536	4	Over 25; watery	20½

From these observations the hypothesis was drawn up that the liverless animal, if supported with adequate glucose, dies of hemorrhage due to failure of the coagulation mechanism.

In further attempt to elucidate the factor or factors responsible for the coagulation defect, determination of the fibrinogen concentration of the plasma and platelet counts were carried out at intervals after hepatectomy. Fibrinogen was determined after sodium sulfite precipitation, thereby not depending upon the clotting mechanism for its isolation. The results of these determinations are seen in Tables III and IV.

The profound depression of the fibrinogen concentration is striking, uniformly observed, and cannot be accounted for by hematocrit change. Simultaneously a marked reduction in peripheral platelet counts occurs.

TABLE III. PLASMA FIBROGEN CONCENTRATION AFTER HEPATECTOMY
(Animal Supported With Glucose Only)

	PLASMA FIBRINOGEN (GM. %)				
DOG NUMBER	1285	12275	226	3126	536
Preoperatively	0.44	0.47	0.37	0.65	0.40
Hours postoperatively					
12	0.23	0.22	0.15	0.36	0.18
16	0.17	0.08	0.11	0.32	0.10
20	Died (hemorrhage)	0.04	0.04	0.23	0.06
Per cent of preoperative value present terminally	39%	8.5%	11%	35%	15%

TABLE IV. PLATELET COUNTS AFTER HEPATECTOMY
(Animal Supported With Glucose Only)

	PLATELET COUNTS ($\times 10^3$)		
DOG NUMBER	12275	226	536
Preoperatively	264	124	134
Hours postoperatively			
12	32	29	65
16	46	6	42
20	–	–	21
Per cent of preoperative value present terminally	17%	5%	16%

The available evidence suggests that platelets are the carriers of antifibrinolysin.[7] Elevated fibrinolytic activity has been noted in patients with severe thrombocytopenia. Thus the possibility suggests itself that the thrombocytopenia observed in liverless dogs may result in increased fibrinolytic and fibrinogenolytic activity due to lack of the usually present antifibrinolytic substance. This increased fibrinolytic activity, in turn, could be responsible for the very rapid drop in plasma fibrinogen concentration. The plasma fibrinogen concentration as seen in Table III falls much too rapidly to be accounted for by simple fibrinogen turnover[2] even in the absence of the liver.

A crude fibrinolysis assay was carried out in 3 dogs in which the post-hepatectomy clots were incubated and lysis time recorded. The clots lysed more and more quickly as later samples were obtained but the determination was not thought reliable since the clots themselves became progressively poorer after hepatectomy.

One of our objectives in seeking the cause of death in the hepatectomized dog was to find means of supporting the animal in addition to glucose. It was hoped this would prolong the dog's life and hence allow further study of the metabolic derangements of hepatectomy.

One dog was given large quantities (1,200 c.c.) of whole blood following hepatectomy. This animal lived 29 hours and just prior to death the prothrombin time was 12 seconds. While showing that the survival period post-hepatectomy could be lengthened by transfusion of whole blood, the basic objective had not been gained since the infusion of huge quantities of whole blood completely masked alterations in concentration of any individual plasma constituents which might give further information to the cause of death when blood volume was maintained.

A solution of dog fibrinogen was prepared and following hepatectomy 2.4 Gm. of fibrinogen were infused in a dilute solution for the first 12 hours. Sixteen hours following hepatectomy the prothrombin time was 30 seconds. This did not represent complete correction of the coagulation defect but was a striking improvement resulting from infusion of a single component.

Since concentrated serum albumin (human) is readily available as a source of antifibrinolysin, 50 Gm. were administered to each of 2 dogs during the first 12 posthepatectomy hours, and to each of 2 other dogs during their entire survival period. The fibrinogen concentrations in these dogs are shown in Table V. While fibrinogen concentration still fell, an average of 43 per cent of the preoperative concentration was still present at 20 hours, while in 4 animals receiving glucose only, 17 per cent remained at this time.

TABLE V. PLASMA FIBRINOGEN CONCENTRATION
(Animals Supported With Glucose and Human Serum Albumin)

	PLASMA FIBRINOGEN (GM. %)			
DOG NUMBER	136	1166	1176	2136
Preoperatively	0.42	0.49	0.51	0.27
Hours postoperatively				
12	0.30	0.21	0.29	0.21
16	0.18	0.16	0.14	0.25
20	0.13	0.15	0.13	0.22
24	-	0.15	-	-
28	-	0.19	-	-
Per cent of preoperative value present terminally	31%	39%	26%	82%

In an effort to eliminate the possibility of the aforementioned improvement being a nonspecific protein effect, a purified antifibrinolysin solution was prepared by the method of Loomis[1] containing only 0.18 Gm. of protein per liter. During the first 12 posthepatectomy hours, 875 c.c. of this preparation were administered to each of 2 liverless dogs. The fibrinogen concentration at 20 hours was 58 per cent of the preoperative level in one dog, but in the other it was not significantly different from the glucose-supported animals. No conclusion can be drawn from these few observations, particularly since no antifibrinolysis titer was performed on the solutions administered so that their relative activities can be compared.

SUMMARY AND CONCLUSIONS

1. The liverless dog when supported by adequate glucose infusion, with rare exceptions, dies of hemorrhage.

2. This hemorrhage is due to a failure of the coagulation mechanism; coagulation time and prothrombin time become infinite.

3. There is profound depletion of fibrinogen and platelet concentrations in the liverless dog.

4. The coagulation defect can be improved and survival time increased by administration of whole blood, serum albumin, and possibly antifibrinolysin to the liverless dog.

5. Speculation suggests that reduction in antifibrinolytic factors may parallel the reduction in platelets thus allowing fibrinolytic preponderance with resultant lysis of circulating fibrinogen as well as preformed clots.

6. Further progress in elucidating the biochemical changes which result from extirpation of the liver will be made only when the coagulation defect can be corrected without administering materials which will mask biochemical alterations.

REFERENCES

1. Loomis, E. C., Ryder, A., George, C., Jr.: Fibrinolysin and Antifibrinolysin: Biochemical Concentration of Antifibrinolysin, Arch. Biochem. **20**: 444, 1949.
2. Madden, R. E., and Gould, R. G.: Turnover Rate of Fibrogen in the Dog, J. Biol. Chem. **196**: 641, 1952.
3. Mann, F. C.: The Effects of Complete and Partial Removal of the Liver, Medicine **6**: 419, 1927.
4. Mann, F. C., and Magath, T. B.: The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, Arch. Int. Med. **30**: 171, 1922.
5. Markowitz, J.: Experimental Surgery, Baltimore, 1949, Williams & Wilkins Company.
6. Markowitz, J., and Soskin, S.: A Simplified Technique for Hepatectomy, Proc. Soc. Exper. Biol. & Med. **25**: 7, 1927.
7. Stefanini, M., and Murphy, I. S.: Human Platelets as Source of Antifibrinolysin, J. Clin. Invest. **35**: 355, 1956.

THE INHIBITION OF CLOTTING BY CONGO RED

JOSEPH M. MILLER, M.D.,* DEBORAH A. JACKSON, B.S.,** AND CHARLES S. COLLIER,** FORT HOWARD, MD.

(From the Surgical Service and General Medical Research Service, Veterans Administration Hospital)

CONGO red has been reported to induce coagulation of the blood.[1] The evidence substantiating the observation, however, has been clinical in nature. The fibrin clot system provides an easy way to test the fundamental concept. The following experiment demonstrated that Congo red inhibits the formation of a fibrin clot when thrombin acts upon fibrinogen.

MATERIALS

Bovine Fibrinogen (Armour).—The fibrinogen was weighed, ground in a mortar with a small amount of borate buffer, and diluted with borate buffer to make a 0.5 per cent solution. The 0.25 per cent solution and the 0.125 per cent solution was made by dilution with borate buffer. The solutions were made just before they were used.

Thrombin, Hemostatic Globulin (Lederle), 4 Per Cent in a 0.05 Normal Acetate Buffer Solution.—A 0.05 N acetate buffer solution was made by dissolving 0.68 Gm. of sodium acetate in 100 ml. of distilled water. A 4 per cent stock solution of the thrombin in the acetate buffer solution was prepared. The reaction was adjusted to a pH of 5.8 with hydrochloric acid. Not more than 100 ml. of the solution was prepared at one time since it had a tendency to become contaminated with molds. The solution was stored in a refrigerator when it was not being used. An 0.8 per cent solution of the stock preparation was made by dilution with the borate buffer solution at a pH of 7.2 to make the fibrin clots. The solution was prepared just before it was used.

Borate Buffer Solution.—The borate buffer solution was made as follows. Boric acid, 11.1 Gm., was dissolved in a small amount of warm distilled water. Sodium borate ($Na_2B_4O_7 \cdot 10\ H_2O$), 7.0 Gm., and 9.0 Gm. of sodium chloride were added and dissolved. Distilled water to make 1,000 ml. was added. The solution was adjusted to a pH of 7.2 to 7.4 with hydrochloric acid.

Solution of One Per Cent Congo Red.—The various dilutions were made just before they were used.

Received for publication Feb. 15, 1957.

*Surgical Service, Veterans Administration Hospital.
**General Medical Research Service, Veterans Administration Hospital.

METHOD

Congo red, 0.1 ml. of the various dilutions, was added to 0.4 ml. of either a 0.125, a 0.25, or a 0.5 per cent solution of fibrinogen and the solutions were shaken. Thrombin, 0.1 ml. of an 0.8 per cent solution, was added immediately.

RESULTS

The results (Table I) indicated that Congo red inhibited the conversion of fibrinogen to fibrin by thrombin. The inhibition was dependent upon the strength of the solution of Congo red and the concentration of fibrinogen since the amount of thrombin used was standard throughout the experiment. Apparently a stoichiometric relationship existed between the Congo red and the fibrinogen.

TABLE I. INHIBITION OF CLOTTING BY CONGO RED

PER CENT CONGO RED 0.1 ML.	FIBRINOGEN 0.125 PER CENT (50 MG./40 ML.) 0.4 ML.	FIBRINOGEN 0.25 PER CENT (50 MG./20 ML.) 0.4 ML.	FIBRINOGEN 0.5 PER CENT (50 MG./10 ML.) 0.4 ML.
1.0	0	0	0
0.1	0	0	0
0.01	0	+	+
0.001	+	+	+
0.0001	+	+	+
0.00001	+	+	+
0.000001	+	+	+

+—Clot present.
0—Clot not present.

SUMMARY

Congo red had the ability to inhibit the formation of fibrin clots when thrombin was added to fibrinogen. An apparent stoichiometric relationship was present between the Congo red and the fibrinogen in the reaction.

REFERENCE

1. Graves, R. C., and Kickham, C. J. E.: Congo Red for the Control of Bleeding, New England J. Med. **214**: 782-783, 1936.

MALIGNANT NEOPLASMS OF THE DUODENUM

Report of Five Cases

George L. Jordan, Jr., M.D., and Michael E. DeBakey, M.D., Houston, Tex.

(From the Cora and Webb Mading Department of Surgery, Baylor University College of Medicine, and the surgical services of the Veterans Administration, Methodist, and Jefferson Davis Hospitals)

SINCE the original description of carcinoma of the duodenum by Hamberger[8] in 1746, numerous publications have appeared, but many are reports of a single case, and the total experience of a single institution has rarely exceeded 15 cases.[2, 5] Consequently, a review of the world literature by Brenner and Brown[1] in 1955 resulted in collection of only 474 cases. Kleinerman and coworkers[10] estimated the incidence at necropsy to be 0.035 per cent, based upon a collected series of 487,695 post-mortem examinations. Other malignant lesions of the duodenum are extremely rare. An accurate incidence of lymphosarcoma of the duodenum is difficult to obtain, as many cases are included in reports concerning lymphosarcoma in other parts of the body. However, it is probably next in frequency to carcinoma, and the ratio of carcinoma to sarcoma has been estimated to be approximately 10 to 1.[6] Weinstein and Roberts[17] were able to collect only 28 cases of leiomyosarcoma from the world literature in 1953, and carcinoid tumors were even rarer; only 21 cases have been collected by Diffenbaugh and Anderson.[3] Whereas 45 per cent of all carcinomas of the small intestine occur in the duodenum,[14] the sarcomas and carcinoid tumors occur much more frequently in other parts of the small intestine. Thus, many articles concerning lymphosarcoma of the small intestine fail to include any instances of duodenal involvement, and only 4 per cent of all carcinoid tumors of the small intestine occur in this location.[3, 16]

The present report concerns 5 primary tumors of the duodenum which we have encountered during the past 3 years, 3 of which were carcinomas, one a reticulum cell sarcoma, and one a carcinoid tumor.

Case Reports

Carcinoma.—

Case 1: A Negro man, 59 years old, was admitted to the Veterans Administration Hospital on April 4, 1953, with a history of weakness, nocturia, edema of the ankles, and loss of 30 pounds in weight during the preceding 4 months. He had no symptoms referable to the gastrointestinal tract. Twenty-one years before admission he had had a cerebrovascular accident, which resulted in left hemiparesis.

On admission the blood pressure was 160 mm. Hg systolic and 90 mm. Hg diastolic. Systolic murmurs could be heard at the aortic and mitral areas, with a short, soft diastolic

Received for publication Jan. 31, 1957.

murmur most audible at the apex. A smooth, slightly tender liver was palpated 3 finger-breadths below the right costal margin. The tip of the spleen was also palpated. There was weakness of the left upper and lower extremities.

Laboratory studies revealed the hemoglobin to be 4 Gm. per 100 ml., erythrocyte count 2,170,000 cells per cubic millimeter, hematocrit 15 per cent, reticulocyte count 14.2 per cent, total proteins 5.4 Gm. per 100 ml., with 3.1 Gm. per 100 ml. of globulin, prothrombin time 95 per cent, alkaline phosphatase 8 units, thymol turbidity 1 unit, serum bilirubin 0.9 mg. per cent, Bromsulphalein retention 31 per cent in 30 minutes. Results of other tests, including blood urea nitrogen, studies of the bone marrow, sickle cell preparations, and examinations for Bence Jones protein, failed to reveal a cause for the anemia, although on one occasion a fecal examination showed occult blood.

Proctoscopic examination and roentgenographic study of the lower gastrointestinal tract following ingestion of barium failed to reveal any abnormalities. An upper gastrointestinal series demonstrated suggestive evidence of a duodenal ulcer, with slight deformity of the bulb.

Following blood transfusions, the hemoglobin concentration returned to normal levels. A preoperative diagnosis of gastrointestinal malignant disease of undetermined site was made. On April 24, 1953, an exploratory laparotomy revealed a polypoid tumor, which measured approximately 4 cm. in diameter and arose just inferior to the ampulla of Vater. No metastatic lesions were seen, and biopsies from adjacent lymph nodes failed to demonstrate carcinoma. The first, second, and third portions of the duodenum were resected. The stump of the fourth portion of the duodenum was closed, and gastrointestinal continuity was re-established in end-to-side pancreatocholedochojejunostomy and end-to-end gastrojejunostomy. Pathologic examination revealed a columnar cell carcinoma extending through the muscular coat of the duodenum.

Postoperatively, a hematoma requiring drainage developed in the presacral space below the peritoneal reflection; no etiologic factors could be ascertained. The anastomoses in the upper portion of the abdomen were seen to be healing primarily. A fecal fistula also developed postoperatively, but it closed spontaneously within a few days. Thereafter, the patient did well, but he was forced to remain in the hospital until July 15, 1953, because of persistent weakness and inability to receive nursing care at home.

On March 5, 1954, he was readmitted with a mass in the superior portion of the old abdominal incision, which he had noted one month previously. Biopsy revealed metastatic adenocarcinoma, and on March 8, 1954, wide excision of this area was performed. He was discharged on March 19, 1954, after an uneventful convalescence.

The patient had no further complaints referable to this lesion, but he was admitted for the last time on Nov. 4, 1954, for treatment of seizures involving the left side of his body, and he died on Nov. 25, 1954. Necropsy revealed the cause of death to be thrombosis of the right middle cerebral artery and bilateral pneumonia. Metastatic carcinoma was found in lymph nodes in the right upper quadrant of the abdomen and a metastatic lesion in the duodenal stump, which had not been suspected clinically.

Case 2: A white woman, 71 years old, was admitted to Methodist Hospital on Oct. 14, 1956, with a history of vomiting of 3 years' duration. At the time of onset, episodes of nausea, relieved by vomiting, occurred every 5 to 6 weeks, but they had increased in frequency until the time of admission, when she suffered attacks twice each week. Fruit, celery, and apples seemed to precipitate attacks. She had no abdominal pain. She had been a known hypertensive since 1942.

On admission the blood pressure was 220 mm. Hg systolic and 95 mm. Hg diastolic. Results of the usual laboratory examinations were within normal limits except for hemoglobin of 9.2 Gm. per 100 ml. An upper gastrointestinal series revealed a filling defect in the third portion of the duodenum (Fig. 1).

The patient was prepared for operation by administration of blood transfusions, which resulted in a rise in hemoglobin to 12.9 Gm. per 100 ml., and on Oct. 16, 1956, an exploratory laparotomy was performed with a preoperative diagnosis of tumor of the small intestine.

A lesion was found in the third and fourth portions of the duodenum. This portion of the intestine was excised, and the defect repaired by end-to-end anastomosis. Pathologic examination of the specimen revealed a soft, sessile, fungating, papillary mass which measured approximately 5 cm. in length (Fig. 2). The microscopic diagnosis was adenocarcinoma of the duodenum with infiltration through the walls of the intestine and involvement of the serosal surface. The patient was discharged on Oct. 27, 1956, after an uneventful postoperative course.

Fig. 1.

Fig. 2.

Fig. 1.—Case 2. The roentgenographic appearance of the carcinoma—a filling defect in the third and fourth portions of the duodenum.
Fig. 2.—Case 2. A papillary carcinoma of the duodenum.

Case 3: A Negro man, 39 years old, was first admitted to the Veterans Administration Hospital on June 5, 1956, complaining of dull aching lower abdominal pain of 7 months' duration. He had lost 12 pounds in weight. The only abnormal physical finding was slight tenderness in the right lower quadrant of the abdomen. The results of the usual laboratory tests were within normal limits, as were roentgenographic studies of the upper and lower gastrointestinal tract after ingestion of barium and a cholecystogram. No definite diagnosis was made.

The patient remained asymptomatic following discharge on June 14, 1956, until the day prior to admission on Aug. 24, 1956, when he suddenly experienced severe upper abdominal pain, which radiated to the back and was associated with nausea and vomiting. He had passed a tarry stool 2 weeks prior to admission but had had no associated symptoms. Physical examination was within normal limits except for mild generalized abdominal tenderness and a palpable liver 1½ fingerbreadths below the costal margin.

The hemoglobin was 9.5 Gm. per 100 ml. and hematocrit 33 per cent. Hematologic studies demonstrated microcytic red cells with hypochromia. Tests of liver function, febrile agglutinations, serum amylase determinations, and sickle cell preparations were reported to be within normal limits. An upper gastrointestinal roentgenographic study demonstrated a

Fig. 3.—Case 3. The roentgenographic appearance of the carcinoma of the duodenum. There is destruction of the mucosal pattern with areas of narrowing of the lumen of the intestine.

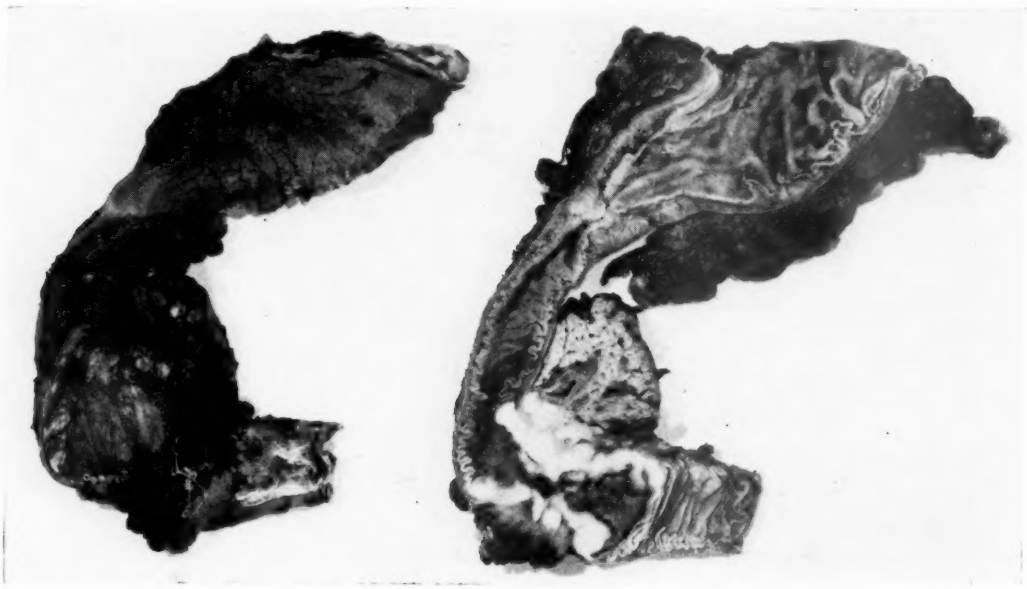


Fig. 4.—Case 3. The surgical specimen removed by pancreatoduodenal resection. There is an annular ulcerating tumor of the third portion of the duodenum.

deformity of the duodenal bulb, but no active ulcer crater was visualized. Transfusions and an ulcer diet relieved the symptoms, and the patient was discharged on Sept. 20, 1956, with a diagnosis of suspected duodenal ulcer.

The patient remained well until Oct. 1, 1956, when anorexia and malaise developed. One week later jaundice developed. He was admitted to the hospital for the third time on Oct. 15, 1956. Physical examination revealed icterus and a slightly enlarged, tender liver. The hemoglobin was 9 Gm. per 100 ml., serum bilirubin 8.8 mg. per cent, alkaline phosphatase 15.7 units, cephalin flocculation 0, thymol turbidity 2 units, prothrombin time 75 per cent.

A diagnosis of homologous serum jaundice was made, and treatment was instituted. Three weeks of treatment resulted in no clinical improvement and no change in the liver function tests. A mass became palpable in the right upper abdominal quadrant, and a second gastrointestinal series showed irregularity of outline of the horizontal portion of the duodenum with destruction of the mucosal pattern and areas of pronounced narrowing (Fig. 3). A diagnosis of primary carcinoma of the duodenum was tentatively made. Laparotomy on Nov. 14, 1956, disclosed a large mass arising from the third portion of the duodenum, measuring approximately 10 cm. in diameter, and involving the transverse mesocolon and posterior parietal peritoneum of the right upper abdominal quadrant. As no distant metastases were found, a pancreatoduodenectomy was performed with removal of 50 per cent of the stomach, the entire duodenum, the head of the pancreas, a portion of the transverse mesocolon, and a portion of the posterior parietal peritoneum from the right upper abdominal quadrant. Gastrointestinal continuity was re-established by the technique of Waugh.[15] Pathologic examination of the specimen revealed an annular ulcerating tumor of the duodenum that extended from the ampulla of Vater into the fourth portion of the duodenum (Fig. 4). Microscopic examination revealed a highly anaplastic carcinoma but no metastases of the lymph nodes. The patient was discharged on Dec. 3, 1956, after an uneventful postoperative course.

Comment: Dixon,[4] who correlated symptoms produced by duodenal carcinoma with morphologic characteristics of the lesion, divided them into 4 main groups: (1) obstructing lesions, which produce vomiting; (2) ulcerating lesions, which bleed and produce melena with secondary anemia; (3) lesions that penetrate into the pancreas and produce a gnawing pain that is usually not relieved by food or alkali; and (4) lesions that encroach upon the ampulla of Vater and produce symptoms suggestive of pancreatic carcinoma. Physical examination usually reveals nothing abnormal in the early stages, and the presence of a palpable mass denotes an advanced lesion.

Roentgenographic examination is the best means of diagnosis, but lesions are often overlooked because of difficulty in proper visualization of this area and failure of the roentgenologist to examine the distal portion of the duodenum carefully unless the clinician suspects a lesion in this region. Thus, in Case 3 the lesion was seen only in the roentgenograms made after the third barium study, but could be visualized in retrospect in the roentgenograms taken in June, 1956, which had been reported as normal.

The cases reported illustrate the usual symptoms produced by these tumors, as well as the common pathologic classification of polypoid, fungating tumors, and scirrhous, annular, stenosing tumors. The latter type predominates. The tumors are also classified according to location as supra-ampullary, periampullary and infra-ampullary. Approximately 60 per cent occur in the periampullary region. This high percentage in the second portion of the duodenum could be attributable to inclusion of some Vaterian carcinomas arising from the pancreatic or bile ducts.[2] Our first case was a periampullary lesion and the second and third infra-ampullary lesions. Whereas the periampullary region was involved in Case 3, the lesion arose from the third portion of the duodenum and the periampullary region was involved only after the tumor had grown large.

Lymphosarcoma.—A Negro man, 46 years old, was admitted to Jefferson Davis Hospital on Oct. 13, 1953, with a complaint of constant cramping pain in the left upper abdominal quadrant for 2 months, extending into the periumbilical and left lumbar regions. The pain

was accentuated by ingestion of food and occasionally was accompanied by nausea and vomiting. The only abnormal physical findings on admission were tenderness in the periumbilical and left lumbar regions and an indistinct mass in the left upper abdominal quadrant.

The hemoglobin, white blood cell count, differential count, and results of urinalysis were within normal limits. A gastrointestinal roentgenographic series showed narrowing and effacement of the mucosal pattern of the duodenum and the first few inches of the jejunum, with dilatation of a segment of duodenum. Lymphosarcoma or direct extension from a primary pancreatic neoplasm was considered to be the most likely diagnosis.

On Oct. 19, 1953, abdominal exploration revealed the fourth portion of the duodenum and the first 3 inches of the jejunum to be thick, indurated, and extremely injected. Specimens for biopsy were taken from the involved portion of the jejunum and from regional lymph nodes, and duodenojejunostomy was performed side-to-side in the second portion of the duodenum. An appendectomy was also performed. Microscopic examination revealed chronic nonspecific inflammation of the jejunum and lymph node. The postoperative course was uneventful, and the patient was discharged from the hospital on the ninth postoperative day.

Nausea and vomiting recurred 48 hours following discharge, and the patient was readmitted on Nov. 1, 1953. Treatment with nasogastric suction and intravenous fluids resulted in prompt subsidence of symptoms, and on November 3 he was able to take oral feedings. Upper gastrointestinal roentgenographic study showed the duodenojejunostomy to be functioning without evidence of obstruction. Barium flowed readily through the second, third, and fourth portions of the duodenum. The patient was discharged essentially asymptomatic Nov. 12, 1953.

Abdominal pain and vomiting, similar to that which he had experienced preoperatively, soon recurred, and by Dec. 26, 1953, the pain had become severe with vomiting 4 to 6 times daily. Weakness increased, and the patient had lost 80 pounds in weight since the onset of his illness. Examination of the abdomen revealed a slightly tender, oblong, irregular mass, which extended across the epigastrium and measured 8 to 10 cm. in length. On Dec. 30, 1953, examination of the gastrointestinal tract following ingestion of barium revealed irregular narrowing and effacement of the mucosal pattern involving the duodenum just beyond the bulb. Barium progressed readily through the duodenojejunostomy but could not be seen in the duodenum distal to the anastomosis.

Re-exploration was deemed advisable, and on Nov. 7, 1954, the fourth portion of the duodenum and the first few inches of the jejunum were resected. The stump of the third portion of the duodenum, which grossly appeared normal, was closed, as was the end of the jejunum. A gastrojejunostomy was then performed, with the use of a loop of the jejunum distal to the duodenojejunostomy. Pathologic examination of the surgical specimen revealed a grayish-red oval ulceration involving the fourth portion of the duodenum measuring 4 by 4 cm., portions of which were covered by necrotic material. In areas the intestinal wall was 1 cm. thick. In addition the proximal jejunum was involved. Microscopic examination showed reticulum cell cytoma involving the entire thickness of the intestinal wall. Regional lymph nodes were also involved.

Postoperative atelectasis developed but responded to tracheal aspiration and administration of antibiotics. Wound dehiscence required secondary closure. Following recovery from the operation a course of roentgen therapy was administered. The patient was discharged on Feb. 17, 1954, and he died at home several weeks later. An autopsy was not obtained.

Comment: The clinical features of lymphomatous tumors are not sufficiently different from those of carcinoma to allow differentiation prior to histologic examination. However, an occasional case has been diagnosed preoperatively by cytologic examination of duodenal contents.[6]

Carcinoid.—

Case 1: A Negro man, 29 years old, was transferred to the Veterans Administration Hospital on March 9, 1953, from another institution. In October, 1952, he experienced upper abdominal pain. Roentgenographic study of the upper gastrointestinal tract following ingestion of barium led to a diagnosis of duodenal ulcer. However, symptoms became increasingly

severe despite medical management. On Feb. 26, 1953, laparotomy revealed a tumor involving the first and second portions of the duodenum and nodules in the liver. As the tumor was considered nonresectable, gastroenterostomy was performed. Biopsy of one of the liver nodules revealed a carcinoid tumor. Because of postoperative psychotic behavior, the patient was transferred to the Veterans Administration Hospital for psychiatric therapy where a diagnosis of schizophrenic reaction, paranoid type, was made. The patient was first seen by the Surgical Consultant on March 13, 1953, when an opening appeared in the mid-portion of his abdominal wound, with profuse drainage of serosanguineous fluid. Secondary closure of the abdominal wound was performed a few hours later, at which time the gross findings reported at the original operation were confirmed. Slides from the original biopsy were obtained by the Pathology Department and the microscopic diagnosis of carcinoid tumor was confirmed. The postoperative course was complicated by a persistent nausea, vomiting, and failure to ingest food. His difficulty was believed to be due partly to malfunction of the gastroenterostomy, and partly to the psychiatric disorder, making cooperation impossible. Two gastrointestinal series performed during this period showed some gastric retention, poor function of the gastroenterostomy, and an ulcer niche in the duodenal bulb.

In April, 1953, the patient was able to tolerate a normal diet, with minimal symptoms. Electroshock therapy considerably improved the psychiatric symptoms. Thereafter he was allowed to go home with instructions to return periodically for further psychiatric management. During this period he continued to have some abdominal distress with occasional vomiting, and on two occasions a diagnosis of partial intestinal obstruction was entertained, but as symptoms subsided within 24 hours, operative intervention was not necessary. A third gastrointestinal series performed on Nov. 13, 1953, showed complete obstruction of the duodenum but good function of the gastroenterostomy. He was discharged from the hospital on Feb. 22, 1954. He had gained weight, was eating well, and his nutrition was considered excellent. He then moved to California. His wife wrote that an operation had been performed late in November, 1954, for intestinal obstruction, and he died on Dec. 2, 1954. No autopsy was performed.

Comment: The number of cases available for study is too small to arrive at any definite conclusions concerning the relative malignant nature of carcinoids of the duodenum as compared with those occurring in other sites. However, only 4 of the 21 cases collected by Diffenbaugh and Anderson[3] had demonstrable metastases. According to them, in most of the reported cases the lesion was removed incidentally in specimens resected for other diseases. Consequently, the information available indicates that most of these lesions are relatively slow growing and have less malignant potential than those located elsewhere in the small intestine. The case herein reported is apparently the fifth metastasizing lesion reported in the literature.

DISCUSSION

There is general agreement that duodenal tumors are best treated by surgical excision. However, metastases are found in 66 per cent of all patients, and adherence of the tumor to vital structures which lie in close proximity to the duodenum may make removal unduly hazardous.[5] Therefore, the resectability rate of duodenal carcinoma has been low—about 20 to 25 per cent. Thus, Shallow and associates[13] found that only 15 of 70 collected cases of infrapapillary duodenal carcinoma had been treated by resection, and the 5-year survival rate is approximately 5 per cent.[1]

Leiomyosarcomas are more slowly growing tumors and, therefore, resection may be accomplished more often. Thus, the tumor was extirpated in 17 of the 28 patients in cases collected by Weinstein and Roberts,[17] 7 of whom were alive at the time of the report, but the longest survival was 3 years.

Many lymphosarcomas are radiosensitive, but we consider excision the treatment of choice, based primarily upon the experience obtained in treatment of similar lesions of the stomach.[9] However, radiotherapy may prolong survival when resection is not technically feasible; therefore, it is advocated whenever there is doubt concerning the adequacy of resection.

The surgical procedure to be employed will depend upon the location of the lesion. Segmental resection is the procedure of choice for lesions of the third and fourth portions of the duodenum, for it is associated with less morbidity and mortality than more radical resection and it appears to give comparable results.[5, 13] However, pancreatoduodenal resection is the procedure of choice for lesions in which the head of the pancreas may be involved. This procedure has not been popular because of the high mortality rate (28 per cent in 123 cases collected by Loggan and Kleinsasser[11] in 1951) and because there are only a few long-term survivals. However, in recent experience with this procedure—for all lesions—mortality rates of 10 to 15 per cent have been reported.[12] In our experience with this procedure during the past few years the mortality rate has been reduced to 12 per cent. This reduction in operative mortality, coupled with reports of 5-year survival rates of 15 per cent for carcinoma of the pancreas and 37 per cent for carcinoma of the ampulla of Vater,[7] justifies the conclusion that this procedure should be employed when necessary to remove any carcinoma in this region.

REFERENCES

1. Brenner, R. L., and Brown, C. H.: Primary Carcinoma of the Duodenum, Gastroenterology **29:** 189-198, 1955.
2. Burgerman, A., Baggenstoss, A. H., and Cain, J. C.: Primary Malignant Neoplasms of the Duodenum Excluding the Papilla of Vater, Gastroenterology **30:** 421-431, 1956.
3. Diffenbaugh, W. G., and Anderson, R. E.: Carcinoid (Argentaffin) Tumors of the Gastrointestinal Tract, Arch. Surg. **73:** 21-37, 1956.
4. Dixon, C. F., Lichtman, A. L., Weber, H. M., and McDonald, J. R.: Malignant Lesions of the Duodenum, Surg., Gynec. & Obst. **83:** 83-93, 1946.
5. Ebert, R. E., Parkhurst, G. F., Melendy, O. A., and Osborne, M. P.: Primary Tumors of the Duodenum, Surg., Gynec. & Obst. **97:** 135-139, 1953.
6. Goldgraber, M. B., Rubin, C. E., and Owens, F. J.: The Cytologic Diagnosis of Duodenal Sarcoma, Ann. Int. Med. **39:** 1316-1322, 1953.
7. Hallenbeck, G. A., Walters, W., Gray, H. K., Priestley, J. T., and Waugh, J. M.: Report on Surgery of the Biliary System and Pancreas for 1954, Proc. Staff Meet., Mayo Clin. **30:** 640-646, 1955.
8. Hamberger, G. S.: Cited by Goldgraber.[6]
9. Jordan, G. L., Jr., Bolton, B. F., Heard, J. G., and Waldron, G. W.: Sarcomas of the Stomach, Surg., Gynec. & Obst. **100:** 453-457, 1955.
10. Kleinerman, J., Yardumian, K., and Tamaki, H. T.: Primary Carcinoma of the Duodenum, Ann. Int. Med. **32:** 451-465, 1950.
11. Loggan, P. B., and Kleinsasser, L. J.: Surgery of the Pancreas, Surg., Gynec. & Obst. (Internat. Abst. Surg.) **93:** 521-543, 1951.
12. Morel, E. L., Janzen, J., and Carter, J.: Pancreaticoduodenal Resection, Am. J. Gastroenterol. **21:** 435-440, 1954.
13. Shallow, T. H., Wagner, F. B., Jr., and Manges, W. B.: Primary Carcinoma of the Infrapapillary Portion of the Duodenum, SURGERY **27:** 348-355, 1950.
14. Silvis, R. S.: Primary Carcinoma of the Duodenum, Am. J. Surg. **88:** 633-644, 1954.
15. Waugh, J. M.: Resection of the Head of the Pancreas and Duodenum: Operative Technique, S. Clin. North America **26:** 941-948, 1946.
16. Weibel, L. A., Joergenson, E. J., and Keasbey, L. E.: A Clinical Study of Small Bowel Tumors, Am. J. Gastroenterol. **21:** 466-477, 1954.
17. Weinstein, M., and Roberts, M.: Leiomyosarcoma of the Duodenum, Arch. Surg. **66:** 318-328, 1953.

CHOLECYSTOLITHOTOMY IN FUNCTIONING GALL BLADDERS

R. C. Long, M.D., and D. R. Webster, M.D., Montreal, Quebec

(From the Department of Surgery of the Royal Victoria Hospital)

THE etiology and pathogenesis of gall-bladder disease with or without stones is not completely understood. However, it appears from available evidence that cholecystitis and cholelithiasis are the result of one and the same pathologic process and that the deposition of stone is the earliest change which occurs. It seems reasonable, therefore, to assume that if the stones could be removed from what is apparently a normal gall bladder that further progression of the disease might be prevented. It is also well recognized that removal of a functioning gall bladder may lead to symptoms which, at times, are very distressing and which may persist until the biliary ductal system is able to adjust itself to the absence of the gall-bladder reservoir. On the other hand, patients with cholelithiasis have a high incidence of complications, some of which, such as acute cholecystitis and choledocholithiasis, carry with them a considerable morbidity and a relatively high mortality. It would seem, therefore, that in a patient who has stones within a functioning gall bladder, simple removal of the stones with the preservation of the gall bladder should be sound procedure.

In a recent article, Mathiesen of Copenhagen reported on a short-term follow-up on a number of cases treated in this manner and the results seemed to indicate that good results might be expected from this procedure. It has been possible to collect a small series of cases which tend to throw some doubt upon this conclusion.

During the years 1932 through 1935, 33 patients were operated upon at the Royal Victoria Hospital with removal of stones from gall bladders without cholecystectomy. It has been possible to obtain a long-term follow-up of 22 of these patients.

In deciding on the procedure several criteria were used. (1) There must be symptoms of gall-bladder disease. (2) There must be radiologic evidence of gallstones. (3) The gall bladder must fill and concentrate the dye well. The Graham Cole test using tetraiodophenolphthalein was used. (4) At operation the wall of the gall bladder must be thin and show no evidence of long-standing disease.

The symptoms which presented in this group of patients are shown in Table I. These symptoms are those commonly associated with disease of the gall bladder. The jaundice present in 2 patients antedated the operative procedure by 2 and 3 years, respectively, and was not considered to be associated with the gall-bladder disease.

Received for publication Jan. 24, 1957.

TABLE I. SYMPTOMS

Right upper quadrant pain	20
Pain radiation	4
Gastrointestinal distress	10
Jaundice	2

In Table II, the age and sex of the patients are shown. The patients are somewhat younger than the normal gall-bladder patient with over half of them being below the age of 40.

TABLE II

Age	
21-30	5
31-40	10
41-50	5
51-60	2
Sex	
Males	2
Females	20

At operation, the abdomen was explored thoroughly in order that other intra-abdominal disease would not be missed. The gall bladder was exposed in the usual manner. Care was taken not to damage the wall of the gall bladder by the injudicious use of clamps or other instruments. An opening was made in the fundus of the gall bladder, the stones were removed and the interior of the gall bladder and the ductal system were examined to ensure that no calculi had been overlooked. The incision in the fundus was then carefully closed with interrupted sutures without drainage and the abdomen closed. It was unfortunate that the wall of the gall bladder was not biopsied nor the bile cultured. In attempting to assess the type of stone, it has been necessary to rely on the clinical appraisal of the operating surgeon, as no stone was subjected to chemical analysis.

Eight cases had only a single calculi while the remaining cases contained multiple stones (Table III).

TABLE III. CHARACTER OF STONES

Single	8
Multiple	14
Cholesterol	7
Bilirubin	5
Mulberry	2
Calcium carbonate	1
Calcified	3
Facetted	4

Of the 33 patients originally undergoing this procedure, it has been possible to obtain a personal follow-up on 22 (Table IV), 19 to 21 years following the original operation. Only 2 patients were free of symptoms referable to

the gall bladder. Nine patients had undergone cholecystectomy, while the remaining 11 had moderate to severe symptoms ranging from recurrent bouts of biliary colic to severe postprandial flatulent dyspepsia and fatty food intolerance.

TABLE IV. FOLLOW-UP

Total number of cases	33
Lost to follow-up	11
Results in Cases Followed	
Number of cases	22
Cholecystectomy	9
Moderate to severe symptoms (no further operation)	11
Asymptomatic	2

All of the patients who had undergone cholecystectomy had been operated upon within 10 years of the original procedure, the earliest within 3 years and one as late as 10 years. Two patients had acute cholecystitis; the remainder had symptoms of chronic gall-bladder disease necessitating operation. In every case, the gall bladder contained stones (Table V).

TABLE V. CHOLECYSTECTOMY

Number of cases	9
Acute cholecystitis with cholelithiasis	2
Chronic cholecystitis with cholelithiasis	7
Interval following original operation	
3 years	1
4 years	2
7 years	3
8 years	2
10 years	1

Cholecystograms were done on 9 of the 11 patients who had symptoms. Of these, 3 showed a nonfunctioning gall bladder, 5 showed poor function but contained stones, while the remaining case continued to show a normal functioning gall bladder with stones (Table VI).

TABLE VI. CHOLECYSTOGRAMS IN PATIENTS WITH SYMPTOMS

Number patients	11
Number cholecystograms	9
Nonfunction	3
Poor function with stones	5
Good function with stones	1

There was no operative mortality nor was there any increased morbidity. In no patient did the sutured gall bladder disrupt nor was there any excess drainage from the wound following operation.

DISCUSSION

The results of this study suggest that gallstone formation is an early stage in the pathologic process which results eventually in the picture of chronic cholecystitis. This is apparently an irreversible process and the fact that the

stones are removed has no effect on the disease process. While metabolic disturbance may be a causative factor in the initial deposit of stones, this too appears to be a permanent rather than a temporary upset and even if a single cholesterol stone is removed, other stones continue to form and eventually the wall of the gall bladder undergoes changes typical of those found in long-standing gall-bladder disease.

Unless the patients are followed over a long period, this fact may not be obvious and this may account for the reports suggesting that simple removal of stones is a sound procedure leaving the patient with a normal functioning gall bladder. It is felt that such a procedure should not be recommended.

SUMMARY

1. Thirty-three patients had the stones removed from normal functioning gall bladders between 1933 and 1935. It is now possible to report a long-term follow-up on 22 of these patients.

2. Only 2 patients are asymptomatic at the present time. Nine patients have undergone cholecystectomy and the remaining 11 continue to have moderate to severe symptoms.

3. All patients who underwent cholecystectomy had recurrent calculi.

4. Of the patients with persistent symptoms, cholecystograms on 9 of these showed calculi in every case.

5. The operation of cholecystolithotomy is not recommended in the treatment of cholelithiasis.

REFERENCE

Mathiesen, Frits R.: Cholecystographic Appearances in 133 Cases Following Cholecystolithotomy, Acta. chir. scandinav. **104**: 56-64, 1952.

RELAPSING PANCREATITIS IN ALCOHOLIC AND NONALCOHOLIC PATIENTS

JACK A. THOMPSON, M.D., JOHN R. DERRICK, M.D., AND JOHN M. HOWARD, M.D., ATLANTA, GA.

(From the Department of Surgery, Grady Memorial Hospital, and Emory University School of Medicine)

THE frequency of recurrent pancreatitis in association with biliary tract disease or chronic alcoholism has been known for several years.[1] Clinical experience has demonstrated that the patients with gallstones frequently have a favorable outcome following correction of the biliary tract pathology,[3, 6] while alcoholic patients with pancreatitis continue to have recurrent attacks, uninterrupted by current forms of treatment.[3, 5] While there have been several reports in which specific studies have been made regarding cholecystic disease in association with pancreatitis, the difficulties in obtaining an accurate alcoholic history have led to a paucity of information regarding the fate of the alcoholic patient with pancreatitis.

Knowledge of the natural course of pancreatitis in the alcoholic or in the patient with gallstones is further confused by the frequent failure in many large series to contrast the clinical background of patients in private hospitals with that of patients treated in hospitals serving the indigent population where a high incidence of alcoholism is encountered. If accurate information regarding the natural course of pancreatitis and a fair evaluation of method of treatment is to be made, it is essential that over-all statistics include the alcoholic intake of the patients and the presence or absence of gallstones as a basis for prognosis for the individual patient. The results of treatment can be predicted by clinical determination of these two factors.[3]

During the years 1948 to 1955, 89 patients with acute pancreatitis were observed at Grady Memorial Hospital, a hospital which serves the vast majority of the indigent of this area. An accurate alcoholic history was solicited from the patient and his family after the diagnosis of acute pancreatitis had been established. The diagnosis of acute pancreatitis was accepted only when made by (1) an elevated serum amylase concentration associated with clinical findings compatible with pancreatitis, (2) laparotomy, or (3) necropsy. Treatment was varied in each instance in accordance with the changing trends of the period and was based primarily on the concept of decreasing pancreatic secretion and providing general support to the individual. After discharge, if further surgical intervention was not indicated, the patients were either seen intermittently in the various outpatient clinics or were lost to follow-up until a severe episode again forced hospital admission. In several instances, follow-up was not obtained until the current follow-up study was undertaken.

Received for publication Feb. 11, 1957.

Seventy-six patients survived the initial episode; while 13 died (Table I), a mortality of 14.6 per cent. Six patients have died since their initial admission, 4 presumably of pancreatitis (2 diagnoses verified at post mortem) and 2 of unrelated causes. Of the initially surviving 76, it has been possible to follow a total of 61 for periods varying from 1 to 7 years with an average follow-up of 33 months.

TABLE I. ACUTE PANCREATITIS—MORTALITY 1948 TO 1955

PATIENTS	TOTAL NUMBER	SURVIVALS	DEATHS	MORTALITY RATE (PER CENT)
Male	43	34	9	20.9
Female	46	42	4	8.7
Total	89	76	13	14.6

The following data are based on the results of evaluation of this group of patients. No attempt has been made to ascribe etiologic significance to various factors existing in the clinical background, but merely to point out and establish statistically the high rate of failure of treatment in the indigent group where a high incidence of alcoholic indulgence and poor dietary intake is more likely.

The significance of an alcoholic background is often difficult to assess, as there is a natural reluctance on the part of the patient to admit the ingestion of alcohol. In this group of 61 survivors of the initially proved attack, special care was taken to determine the degree of alcoholic consumption. The establishment of a pancreatic follow-up clinic and the fact that this is the only institution in the area supplying emergency care for the indigent aided considerably in obtaining this information.

RESULTS

Pancreatitis in the indigent patient is a recurring and often fatal or disabling disease. Of the 89 patients in this series, 13 died of pancreatitis during their initial hospitalization and 4 have subsequently died of pancreatitis, a total mortality of 19 per cent. Including the 4 patients who died of secondary attacks, 51 per cent of the survivors of the initial attack are known to have had recurrence of the disease, and if those lost to follow-up are eliminated, the recurrence rate rises to 58 per cent. Of those followed, 29 patients either gave a history of a heavy ingestion of alcohol or have come to the hospital in an intoxicated state. Seventeen specifically denied the use of alcohol and can be classified as abstainers. In 15 instances, the alcoholic background could not be reliably established and these individuals were placed in the unknown category. Of the 13 who died initially, 6 were alcoholic, 3 were abstainers, and the alcoholic history could not be obtained in 4. One of the 4 subsequent deaths due to pancreatitis occurred in an alcoholic patient. The most significant finding is presented in Table II. Twenty-one of the 29 surviving alcoholics have had recurrence of incapacitating symptoms of acute pancreatitis (72 per cent), while in the nonalcoholic the rate of relapse is only 29 per cent. The recurrence rate of the unknown group is 60 per cent, remarkably close

to the average of the over-all series. This high rate of failure in the unknown group may represent inability to identify all of the alcoholics. Pseudocysts developed in 5 of the alcoholic patients (Table III), and one patient has developed pancreatic calcification without cyst formation. None of the nonalcoholic patients has subsequently developed either of these complications and in the unknown group 2 pseudocysts have developed.

TABLE II. RELAPSING PANCREATITIS—RELATION TO ALCOHOLIC INTAKE

ALCOHOLIC INTAKE	FOLLOW-UP OF SURVIVING PATIENTS		
	RECURRENCE	WELL	TOTAL
Chronic alcoholism	21 (72%)	8 (28%)	29
Nonalcoholic	5 (29%)	12 (71%)	17
Unknown	9 (60%)	6 (40%)	15
Total	35 (57%)	26 (43%)	61

TABLE III. RELAPSING PANCREATITIS—COMPLICATIONS IN RELATION TO ALCOHOLIC INTAKE

ALCOHOLIC INTAKE	NUMBER OF PATIENTS FOLLOWED—61		
	PSEUDOCYST	PANCREATIC CALCIFICATION	TOTAL
Chronic alcoholism	5	1	6
Nonalcoholic	0	0	0
Unknown	2	0	2

The presence of gallstone disease has been recognized as a factor not only in the etiology of pancreatitis, but also as a factor significantly influencing the prognosis.[3] In the current series, the diagnosis of biliary disease was limited to those patients in whom gallstones could be identified.

The rate of recurrent pancreatitis in patients with gallstones was 38.5 per cent in those patients who were followed without cholecystectomy for one year or longer after the initial attack (Table IV). The individuals with a normal gall bladder, as demonstrated by cholecystography, had a recurrence rate of 69 per cent, with 24 of 35 patients having a return of symptoms. The unknown group includes those patients in whom adequate cholecystograms were not obtained[4,7] and 3 with microscopic evidence of cholecystitis, but no biliary stones. The rate of failure in this group was 46 per cent, a rate similar to the average incidence of recurrence. Of the 8 patients developing pseudocysts or pancreatic calcification, 6 had normal gall-bladder function without gallstones, one had gallstones, and in one instance the status of the gall bladder is unknown (Table V).

TABLE IV. RELAPSING PANCREATITIS—RELATION TO GALLSTONES
Natural Course of Disease in Patients Without Definitive Surgery for 1 Year or Longer

GALL-BLADDER STATUS	NUMBER OF PATIENTS FOLLOWED—61		
	RECURRENCE	WELL	TOTAL
Lithiasis	5 (38.5%)	8 (61.5%)	13
Normal	24 (69%)	11 (31%)	35
Unknown	6 (46%)	7 (54%)	13

The results of cholecystectomy in patients with gallstones have been encouraging (Table VI), as only 3 patients (30 per cent) have had relapses

TABLE V. RELAPSING PANCREATITIS—PANCREATIC COMPLICATIONS IN RELATION TO GALLSTONES

GALL-BLADDER STATUS	NUMBER OF PATIENTS FOLLOWED—61		
	PSEUDOCYST	PANCREATIC CALCIFICATION	TOTAL
Normal	5	1	6
Lithiasis	1*	0	1
Unknown	1	0	1

*Whether this patient was also an alcoholic is unknown.

following removal of gallstones and these 3 patients had sphincterotomy in addition to cholecystectomy and choledochostomy. Whether the subsequent illnesses in the latter 3 patients were due to failure of cholecystectomy or whether they were additive effects of sphincterotomy cannot be ascertained with certainty. No patient had a recurrence following removal of gallstones except these 3 patients with sphincterotomy. Removal of common duct stones completely relieved the 2 patients in whom they occurred. These findings suggest that removal of gallstones interrupts the tendency to develop recurrent pancreatitis; the effect is particularly striking when the stones are in the common duct.[7]

TABLE VI. RELAPSING PANCREATITIS—RESULTS OF REMOVING GALL BLADDER AND GALLSTONES

GALL-BLADDER STATUS	NUMBER OF PATIENTS		
	RECURRENCE	WELL	TOTAL
Cholelithiasis	3*	7	10
Choledocholithiasis	0	2 (included above)	2
Normal	7	4	11

*Sphincterotomy and normal common duct in all 3 patients.

DISCUSSION

While the surgical literature contains numerous references to the frequency of relapsing pancreatitis in the alcoholic, the previous studies have usually failed to separate and follow the alcoholics as a group. The observations in reviewing this series of patients, where a reasonably accurate alcoholic history has been obtained, indicates that the clinical association of pancreatitis and alcoholism results in a very high rate of recurrence.

The mortality rate of the initial attack in the alcoholic was essentially similar to that of the nonalcoholic and to the patient with an unknown alcoholic intake. The ultimate death rate, however, will probably be higher in the alcoholic, as the frequency of recurrent attacks of pancreatitis leads to additional mortality.[5] The alcoholic who survives the repeated attacks has a higher incidence of pancreatic calcification and pseudocyst formation than does the nonalcoholic.

As has been pointed out in the past, the patient with cholelithiasis has a considerably better prognosis particularly after removal of the gallstones.[3, 5] In this study the rate of recurrence in patients with gallstones was considerably below that of the patients with a normal gall bladder, but this probably reflects a shorter period of follow-up since cholecystectomy repeatedly interrupted the natural course of pancreatitis in those patients with gallstones.

It is apparent that little benefit is obtained from removing a normal gall bladder as these patients continued to have recurrent attacks in a ratio similar to that of the entire group. In the future, evaluation of operative and nonoperative treatment must include a careful consideration of the clinical background of the patient before ascribing success to a particular form of therapy. There are two groups in which the results can be predicted: the alcoholic will have many recurrent attacks; the patient with gallstones as the basis of his disease will usually recover when the biliary tract disease is corrected.

SUMMARY

Pancreatitis as seen in the indigent patient carries a morbidity that is considerably greater than that seen in institutions in which patients in a higher economic status are treated. A review of the clinical background of these patients discloses that a prediction of the fate of the individual can be made by determining the alcoholic intake and the status of the gall bladder. The alcoholic patient has a 72 per cent rate of recurrent attacks with a considerably increased incidence of pancreatic calcification and cyst formation. The ultimate mortality rate in the alcoholic with pancreatitis will undoubtedly increase as the additive effect of secondary attacks accrues.

The patients with gallstones tend to have fewer recurrences as they are usually relieved by the removal of the biliary stones. The rate of relapse prior to correction of the biliary tract disease is considerable, but not as marked as in the alcoholic. Removal of the normal gall bladder does not alter the rate of recurrence.

Pancreatitis is a recurrent disease in the majority of indigent patients, with the alcoholic patient having an extremely poor prognosis.

REFERENCES

1. Gambill, E. E., and Comfort, M. W.: Relapsing Pancreatitis; An Analysis of 27 Cases Associated With Disease of the Biliary Tract, Gastroenterology **11**: 1-33, 1948.
2. Howard, J. M., and Jordan, G. L., Jr.: Relapsing Pancreatitis Secondary to Choledocholithiasis, A. M. A. Arch. Surg. **73**: 960-964, 1956.
3. Kaden, V. G., and Howard, J. M.: Clinical Studies of the Natural History of Pancreatitis, A. M. A. Arch. Surg. **73**: 269-271, 1956.
4. Kaden, V. G., Howard, J. M., and Doubleday, L. C.: Cholecystographic Studies During and Immediately Following Acute Pancreatitis, SURGERY **38**: 1082-1086, 1955.
5. O'Brien, J. J., and Thayer, T. R.: Pancreatitis: Observations of 131 Patients, New England J. Med. **253**: 355-360, 1955.
6. Raker, J. W., and Bartlett, M. K.: Acute Pancreatitis: Fate of the Patient Surviving One or More Acute Attacks, New England J. Med. **249**: 751-757, 1953.
7. Silvani, H. L., and McCorkle, H. J.: Temporary Failure of Gall Bladder Visualization by Cholecystography in Acute Pancreatitis, Ann. Surg. **127**: 1207-1211, 1948.

MUCOID ADENOCARCINOMA OF THE COLON AND RECTUM

EARL F. WOLFMAN, JR., M.D.,* VERNON B. ASTLER, M.D., AND
FREDERICK A. COLLER, M.D., ANN ARBOR, MICH.

(From the Departments of Surgery and Pathology, University of Michigan)

THE enigma of mucoid carcinoma has been discussed from various points of view during the past several decades.[4-6] Many synonyms for this entity appear in the literature. It has been called colloid carcinoma, gelatinous carcinoma, mucin-forming carcinoma, adenocarcinoma mucosum, carcinoma colloides, and myxomatous carcinoma. There is no unanimity of opinion regarding the relative malignancy and prognostic implications of mucoid carcinoma. Parham[5] states that "colloid carcinoma" is usually slow of growth and late to metastasize to lymph nodes and organs. He adds that, although it is histologically less malignant, it is particularly difficult to eradicate because it permeates the tissues. Death is often delayed, but the eventual mortality is greater than in other types of carcinoma. Trimpi and Bacon[6] believe that from a strictly histologic point of view, the disease is less malignant than other types of adenocarcinoma. It is apparent that although the histologic appearance of a malignant tumor has some prognostic value, the true prognostic significance can only be obtained by correlating the histologic data with the clinical course in a large group of patients. This report concerns such a study.

MATERIAL AND METHODS

Mucoid adenocarcinoma may be classified as extracellular or intracellular according to the predominant location of the mucus. The extracellular type is characterized microscopically by lakes of mucus lined by tall columnar cells with basal nuclei; however, these lining cells may be flattened or absent because of glandular distention, necrosis, or spread of the secreted mucus between tissue fibers (Fig. 1). The intracellular form is typified by large numbers of signet-ring cells assuming either a scirrhous or medullary pattern (Fig. 2). In some instances both intracellular and extracellular elements may be present in different portions of the same tumor.

Between July 1, 1940, and June 30, 1949, 880 patients were admitted to the University Hospital and subsequently underwent surgical excision of primary adenocarcinomas from the large intestine and rectum. Follow-up studies have been carried out on all patients over periods of 5 to 16 years; no patients were lost to follow-up. The 880 operations performed included procedures which were known to be only palliative, either because of widespread local involvement or because of the presence of metastatic disease in other viscera, as well as those procedures where all gross tumor was thought to have been removed. Combined abdominoperineal resection was carried out for palliation as well as

Received for publication March 25, 1957.
*Trainee of the National Cancer Institute.

for cure of rectal carcinoma. Specimens from primary lesions were examined by the pathologist at the time of operation. The microscopic sections from lesions which were originally reported to show mucous formation were reviewed at the

Fig. 1.

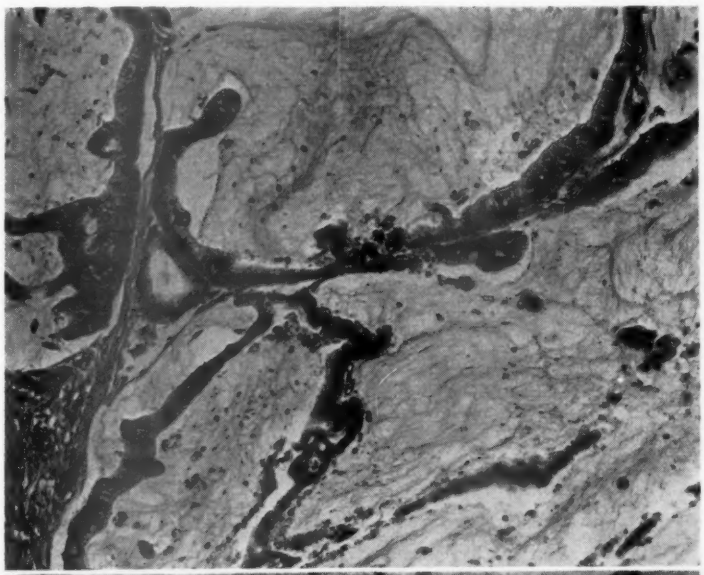


Fig. 2.

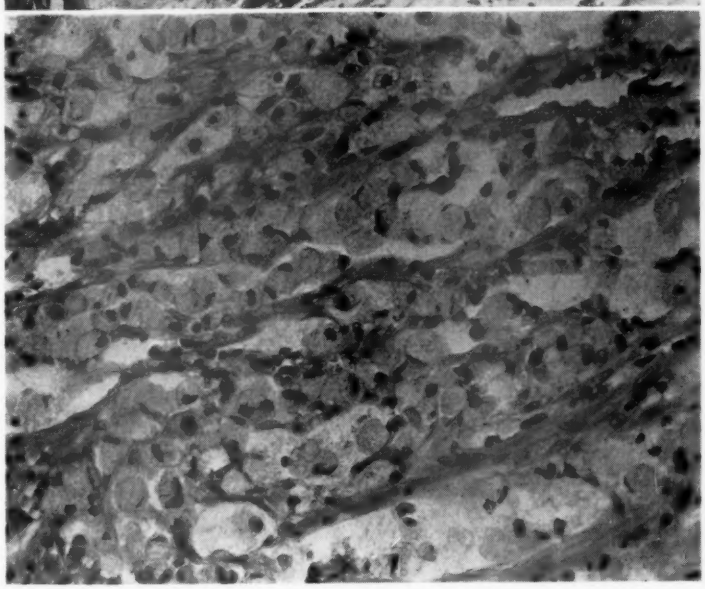


Fig. 1.—Extracellular mucoid adenocarcinoma of the sigmoid colon showing columnar, cuboidal, and flat carcinoma cells. The lakes of extracellular mucinous material have dissected the muscular stroma of the bowel wall (×45, reduced ¼ off).

Fig. 2.—Intracellular mucoid adenocarcinoma of the rectum showing signet-ring cells with large eccentric nuclei and contained mucinous material. Note wide separation of stromal fibers (×130, reduced ¼ off).

time of this study, and the tumors reclassified by the authors and the pathologists. Since some degree of mucous formation is characteristic of adenocarcinoma of the colon and rectum, tumors in this series were classified as mucoid

carcinoma only if microscopic examination showed the major portion of the tumor to contain mucinous material or large numbers of signet-ring cells. The mucoid carcinomas were differentiated as to intracellular or extracellular type, and both mucoid and nonmucoid adenocarcinomas were further classified according to Dukes' classification as modified by Kirklin, Dockerty, and Waugh[3] and reported by Astler and Coller.[1] Finally, the clinical course in each case was reviewed and correlated with the histologic studies.

RESULTS

Incidence.—Of the 880 cases reviewed, 713 (81 per cent) were classified as nonmucoid adenocarcinoma and 167 cases (19 per cent) as mucoid adenocarcinoma. The mucoid adenocarcinomas were classified as extracellular in 146 cases (16.6 per cent) and intracellular in 21 cases (2.4 per cent). At the time of operation, lymph nodes were found to be involved in 44 per cent of the cases of nonmucoid carcinoma, in 38.4 per cent of the cases of extracellular mucoid adenocarcinoma, and 85.7 per cent of the cases of intracellular mucoid adenocarcinoma.

Age and Sex.—The average age of patients with nonmucoid carcinoma was 58.7 years, and of those with mucoid carcinoma, 57.6 years. Of the patients with nonmucoid adenocarcinoma, 425 (59.6 per cent) were men and 288 (40.4 per cent) were women; in the group with mucoid adenocarcinoma, 108 (64.7 per cent) were men and 59 (35.3 per cent) were women.

Symptoms.—There was no appreciable difference in symptoms exhibited by patients with mucoid and with nonmucoid lesions. The most common symptom was rectal bleeding. Other complaints in order of decreasing frequency were abdominal pains and cramps, constipation, diarrhea, tenesmus, bloating, malaise, weight loss, and hemorrhoids.

Operative Mortality.—All patients who died within one month after operation, regardless of cause, were included in this group. There were 63 deaths in the 880 cases, an operative mortality rate of 7.2 per cent.

Survival.—At the time of excision of the primary lesion, positive lymph nodes were found in 388 cases (44.1 per cent), and in another 385 cases (43.7 per cent) it was found that the tumor extended entirely through the bowel wall. Thus, in 87.8 per cent of the patients in this series, the lesions had extended beyond the confines of the bowel wall by the time the patients were first seen

TABLE I. SUMMARY OF 5-YEAR SURVIVAL DATA IN 880 CASES GROUPED ACCORDING TO THE MODIFIED DUKES' CLASSIFICATION

GRADE	NONMUCOID (PER CENT)	MUCOID	
		EXTRACELLULAR (PER CENT)	INTRACELLULAR (PER CENT)
A	100.0	100.0	
B_1	64.8	69.2	
B_2	51.3	38.9	66.6
C_1	33.3	50.0	
C_2	19.2	19.0	27.8

The 5-year survival rate in the nonmucoid B_2 group was 12.4 per cent greater than that in the extracellular B_2 mucoid group. The difference in survival rates in the C_1 extracellular mucoid group and the C_1 nonmucoid group is not significant, since only 2 cases of C_1 extracellular lesions were noted, in one of which the patient survived 5 years.

here. The over-all 5-year survival rate for the 880 cases was 38.4 per cent. The 5-year survival rates among patients with nonmucoid lesions and those with mucoid lesions were 39.4 and 34.1 per cent, respectively. Further subdivision of the mucoid carcinomas demonstrated a 5-year survival rate of 34.2 per cent in cases of extracellular lesions and 33.3 per cent in cases of intracellular lesions. Table I summarizes the survival data on patients whose lesions were grouped according to the modified Dukes' classification.

Fig. 3.—Intracellular mucoid adenocarcinoma of the rectum showing submucosal lymphatic permeation resulting from the mechanical pressure of the large amount of extruded mucin (×75, reduced ¼ off).

DISCUSSION

There is general agreement that the production of mucus by carcinomatous cells indicates functional differentiation and that the mucus is a product of cellular secretion rather than degeneration. Trimpi and Bacon[6] have described several factors in the pathogenesis of mucoid carcinoma which may affect the biologic nature of these tumors. Mucin, the major component of the secretion of mucoid carcinomas, is a mixture of glycoproteins, soluble in water, and precipitated by alcohols and acids. When mucin comes in contact with water it swells to form mucus. Mucus usually appears in the earliest stages of tumor formation. With the extrusion of this material, mechanical pressure within the cell mass increases and apparently leads to separation and dissection of the stroma and to the more rapid local dissemination of the tumor cells, which are less adhesive and tend to break away and float in the mucus. The increased tissue pressure associated with the secretion and extrusion of the mucinous material may also lead to early lymphatic permeation by the carcinoma cells (Fig. 3).

There is a significantly greater 5-year survival rate among patients with nonmucoid B_2 lesions than among those with extracellular mucoid B_2 tumors (Table I). The standard error of the difference between these 2 groups is ±6.4

with an associated P value of 0.054, allowing little probability that this is a fortuitous observation. This discrepancy in survival is most likely related to the secreted mucus. It may be postulated that in the early stages of development, stage A or B_1, the mucoid and nonmucoid lesions show no appreciable difference with regard to prognosis or behavior. The lesions are still confined within the limits of the bowel wall, and radical surgical excision offers equal opportunity for their complete removal. Likewise, when lymph nodes have become involved and the lesion has extended completely through the bowel wall, stage C_2, the prognosis is similar in the 2 types of tumors. Only 2 patients with extracellular mucoid C_1 lesions were present in this series, one of them surviving 5 years. Because of the limited number of cases, the associated 5-year survival rate of this group is not significant. It is the extracellular mucoid adenocarcinoma which has extended completely through the bowel wall without lymphatic involvement, the B_2 lesion, that is more difficult to extirpate than its nonmucoid counterpart. Presumably this is due to the lowered resistance of the pericolic and perirectal tissues to this tenacious liquid substance, mucus, and its contained tumor cells. Consequently, once the tumor has extended through the bowel wall, extensive local spread may occur that is not apparent grossly and so allows the tumor to pass beyond the usual confines of the standard resection. Local recurrences of carcinoma were more common in the extracellular mucoid group than in either the intracellular mucoid or nonmucoid varieties of adenocarcinoma. Therefore, if this type of tumor is suspected or proved to be present, it would be advisable to extend the limits of resection beyond that which is usually carried out for the nonmucoid adenocarcinomas. Meticulous care must be employed when handling extracellular lesions, for they may be quite bulky and gelatinous. Unrecognized contamination of the abdominal cavity by this tumor-containing fluid medium is likely to occur with minor degrees of trauma.

The 5-year survival rates for nonmucoid and extracellular mucoid C_2 lesions are nearly equal. Yet if the rate of distant spread by lymphatic channels were the same for these 2 types, one would expect a considerably lower 5-year survival rate for the extracellular group. The similarity in survival rates indicates that once the regional lymph nodes and channels have become involved, the nonmucoid tumor metastasized to distant areas more rapidly than the extracellular mucoid lesion. The latter, in contrast, remained localized in regional lymph nodes and channels for longer periods.

The intracellular mucoid adenocarcinoma is of relatively infrequent occurrence. The number of cases in this series are few and do not allow definite conclusions; however, certain factors may be noted. All lesions of this type had penetrated through the bowel wall by the time they were first seen. The higher incidence of lymph node involvement (85.7 per cent) at the time of operation is striking. Submucosal lymphatic permeation was frequent. Figs. 4 and 5 show a progressive mortality rate associated with nonmucoid and extracellular mucoid adenocarcinomas over a 5-year period. Fig. 6 shows that the majority

of patients with intracellular mucoid adenocarcinoma succumbed to their disease within the first postoperative year. Indeed, of the 14 deaths in this group, 11 occurred during the first postoperative year, 2 during the second year, and one before the end of the third year. No further deaths or recurrences occurred in this group during the follow-up period. It seems, therefore, that this is a highly malignant type of tumor giving rise to symptoms late in its development and metastasizing primarily via the lymphatic channels. Without treatment its

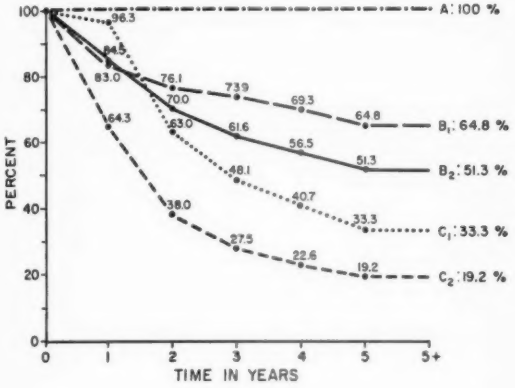


Fig. 4.

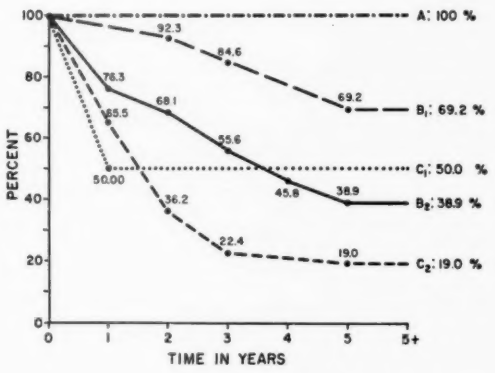


Fig. 5.

Fig. 4.—Graphic year-by-year survival (per cent) in all cases of nonmucoid adenocarcinoma of the colon and rectum seen at the University Hospital from 1940 through 1949 (713 cases). These cases are grouped according to the modified Dukes' classification.

Fig. 5.—Graphic year-by-year survival (per cent) in all cases of extracellular mucoid adenocarcinoma of the colon and rectum seen at the University Hospital from 1940 through 1949 (146 cases). The apparently greater survival rate associated with C_1 lesions as compared to the B_2 group is not significant since only 2 C_1 lesions were noted, one of these patients surviving 5 years.

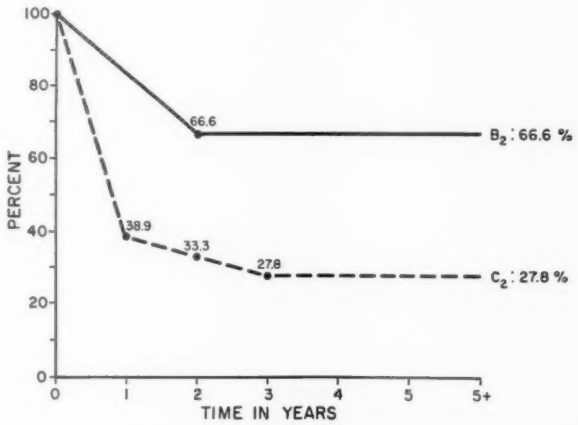


Fig. 6.—Graphic year-by-year survival (per cent) in all cases of intracellular mucoid adenocarcinoma of the colon and rectum seen at the University Hospital from 1940 through 1949 (21 cases). All deaths due to this type of tumor occurred before the end of the third postoperative year, the majority during the first postoperative year.

course is rapid. If radical surgical intervention is carried out early, however, before lymphatic permeation occurs or before distant lymphatic vessels are involved, the prognosis appears even better than for the nonmucoid or extracellular mucoid lesions.

It is clear from the report of Astler and Coller[1] and the evidence obtained in this series that the modified Dukes' classification provides the clinician with an accurate prognostic tool for the evaluation of adenocarcinomas of the colon and rectum (Figs. 4, 5, and 6). Broders' classification, in contrast, is an entirely histologic grade that does not take into account the local extent of the lesion or the presence or absence of distant disease.[2] The histologic grading of tumors is useful as a guide to treatment rather than prognosis; for example, a direct correlation usually exists between the histologic grade of a tumor and its degree of radiosensitivity. The modified Dukes' classification, on the other hand, correlates well with the biologic characteristics of the tumor removed at operation.

SUMMARY

Mucoid adenocarcinomas of the colon and rectum are histologically distinct tumors characterized by the presence of a mucous material, the chief component of which is mucin. The mucus may be primarily extracellular or intracellular.

A study was made of 880 cases in which primary adenocarcinomas were removed from the colon and rectum, between July 1, 1940, and June 30, 1949. Follow-up studies were carried out in all cases over periods ranging from 5 to 16 years. There were 167 cases (19 per cent) of mucoid adenocarcinoma of which 146 (16.6 per cent) were extracellular and 21 (2.4 per cent) were intracellular. There was no significant difference in symptoms or in incidence according to age and sex between the cases of mucoid and of nonmucoid adenocarcinoma. In 87.8 per cent of the patients, operation revealed lesions extending beyond the confines of the bowel wall. The over-all 5-year survival rate in the series of 880 patients was 38.4 per cent. The 5-year survival rates were 39.4 per cent for the group with nonmucoid lesions and 34.1 per cent for those with mucoid lesions. The operative mortality rate for the series was 7.2 per cent. The extracellular mucoid B_2 lesions were accompanied by a significantly lower 5-year survival rate than the nonmucoid B_2 lesions. This is presumably due to the more extensive local spread which occurs after the mucoid material escapes beyond the limits of the bowel wall.

The intracellular mucoid adenocarcinoma is a relatively infrequent tumor that gives rise to symptoms late in its development. The prognosis is favorable if radical excision is carried out early.

The series reported offers further evidence to substantiate the value of the modified Dukes' classification as a prognostic aid in cases of adenocarcinoma of the colon and rectum.

REFERENCES

1. Astler, V. B., and Coller, F. A.: The Prognostic Significance of Direct Extension of Carcinoma of the Colon and Rectum, Ann. Surg. **139**: 846, 1954.
2. Broders, A. C.: The Grading of Carcinoma, Minnesota Med. **8**: 726, 1925.
3. Kirklin, J. W., Dockerty, M. D., and Waugh, J. W.: The Role of the Peritoneal Reflection in the Prognosis of Carcinoma of the Rectum and Sigmoid Colon, Surg., Gynec. & Obst. **88**: 326, 1949.
4. Ochsenhirt, N. C.: The Significance of Mucus Forming Cells in Carcinoma of the Large Intestine and Rectum, Surg., Gynec. & Obst. **47**: 32, 1928.
5. Parham, D.: Colloid Carcinoma, Ann. Surg. **77**: 90, 1923.
6. Trimpi, H. D., and Bacon, H. E.: Mucoid Carcinoma of the Rectum, Cancer **4**: 597, 1951.

MASSIVE HEMORRHAGE FROM DIVERTICULAR DISEASE OF THE COLON

CHARLES D. KNIGHT, M.D., SHREVEPORT, LA.

(From the Departments of Surgery, Highland Clinic and Confederate Memorial Medical Center)

THE occurrence of hemorrhage as a complication of diverticular disease of the colon seems to be fairly well accepted. The occurrence of massive or exsanguinating hemorrhage as a complication of this disease process is not so well appreciated. The incidence of bleeding in diverticular disease varies considerably, but the majority of reports range from 10 to 30 per cent. This reported bleeding usually consists of minimal amounts reported by patients during their historical interview. The occurrence of massive bleeding is apparently rare and its exact incidence is unknown. Published reports, however, indicate that surgeons are encountering this problem more frequently and that its management may constitute a real challenge.

Our interest in this problem has been stimulated by several patients with massive hemorrhage, presumably from colon diverticula, who recently required treatment. We were prompted to review our own cases as well as to survey the literature to ascertain the experience of others with this problem.

SELECTION OF MATERIAL

Two series of patients were reviewed for this report. The first consisted of 185 patients seen at the Highland Clinic and admitted to the Highland Hospital with a proved diagnosis of diverticulosis and/or diverticulitis during the years 1946 through 1955. The second series was made up of 104 patients admitted to the Confederate Memorial Medical Center with a similar diagnosis during the years 1949 through 1955. The case histories in both series were carefully studied and all those with a history of gross rectal bleeding were reviewed to ascertain the etiology of the hemorrhage.

If there was a reasonable cause found for the bleeding other than diverticular disease of the colon, the case was excluded. This eliminated patients who had colonic diverticular disease who also had hemorrhoids, duodenal ulcer, alcoholic gastritis, Hodgkin's disease, colitis, colonic polyps, and so forth. The remaining cases which were selected for more detailed study were those with rectal bleeding presumably due to the colonic diverticula since no other etiology was established.

REVIEW OF CLINICAL DATA

First Series.—Of 185 patients admitted to the Highland Hospital from 1946 through 1955 with a proved diagnosis of diverticulosis and/or diverticulitis, 23

Received for publication Jan. 23, 1957.

gave a history of gross bleeding from the rectum, presumably due to diverticulosis. This is an incidence of 12.4 per cent. Review of these 23 cases showed that they had received complete evaluation of their bleeding and no other possible cause could be found. This evaluation included gastrointestinal x-rays, proctoscopic examination, and study of clotting mechanisms and liver function. The diagnosis was made in 21 of these patients by roentgenographic study of the colon which revealed varying numbers of diverticula present.

TABLE I. DATA ON PATIENTS WITH SEVERE HEMORRHAGE FROM DIVERTICULOSIS (Highland Clinic 1946-1955)

PATIENT	AGE	SYMPTOMS	REMARKS	OUTCOME
1. B. M.	50	Painless rectal bleeding; red to tarry stools; weakness with fainting; occurred intermittently for 15 years	X-ray showed diverticulosis involving entire colon; all other studies within normal limits; bleeding required 18 hospital admissions and 22 pints of whole blood as transfusions over 15 years; had conservative treatment only; refused surgery	Living; no hemorrhage since August, 1955
2. E. M.	61	Diarrhea with stools varying from red to tarry in color; weakness and fainting; similar hemorrhage every 2 years for 15 years	Patient bled massively in spite of transfusion therapy and on the sixth day exploratory laparotomy revealed extensive diverticulosis of the colon and a colon filled with blood; ascending colostomy performed; bleeding stopped and one month later, subtotal colectomy performed with ileosigmoidostomy	Living; no hemorrhage since operation
3. J. H.	67	Massive rectal bleeding with dark blood mixed with bright red blood	X-ray showed extensive diverticulosis involving entire colon; other studies within normal limits; treated with multiple transfusions and patient stopped bleeding after 4 or 5 days; also had coronary heart disease	Lived 1½ years following hemorrhage and died in heart failure
4. J. B.	61	48 hours of diarrhea with dark bloody stools, progressive weakness, and fainting	X-ray showed diverticulosis of descending and sigmoid colons; all other studies normal; hemoglobin 6 Gm.; received 2,500 c.c. blood and stopped bleeding after 3 or 4 days	Living; no hemorrhage since 1952
5. A. W.	74	Signs and symptoms of coronary occlusion; repeated episodes of melena; no hematemesis	Diverticulosis of transverse, descending, and sigmoid colons on previous x-ray; hemoglobin 8 Gm. on admission	Died; autopsy showed cause of death coronary thrombosis; no cause of gastrointestinal bleeding except diverticulosis
6. N. S.	79	Massive rectal hemorrhage; weakness	X-ray showed diverticula of descending and sigmoid colons; other studies normal; hemoglobin 9 Gm.; required multiple transfusions	Living; coronary occlusion in 1954 and recovered
7. J. W.	72	Sudden massive rectal hemorrhage with 4 large bloody stools; marked weakness	Admitted in shock with B.P. 70/50; required multiple transfusions and continued to bleed for several days; x-rays showed numerous diverticula scattered throughout the colon; other studies normal	Living; no hemorrhage since 1951

Two patients had a diagnosis of diverticulosis made at laparotomy. Five patients showed diverticulosis of the entire colon. Proctoscopic examination of one patient showed bleeding from the mouth of a diverticulum. Seven patients of these 23 with rectal bleeding were considered to have massive bleeding in that they showed evidence of shock and/or marked blood loss and/or required 1,000 c.c. or more of whole blood as transfusions. Summarizing data concerning these 7 patients are found in Table I. Four of these 7 patients had diverticulosis of the entire colon while still another one had involvement of the transverse, descending, and sigmoid colons. The other patients had diverticulosis localized to the descending and sigmoid colons. Only one of these patients died and the cause of death was coronary thrombosis. No cause of gastrointestinal bleeding was found at autopsy except diverticulosis. One patient required emergency surgery for massive bleeding and because of the therapeutic problem presented, a brief abstract of his history and course is presented.

E. M., a 61-year-old white man was admitted to the hospital on Feb. 1, 1955, after 60 hours of bloody diarrhea. The stools varied from tarry to bright red in color and there was no history of hematemesis. He had had similar episodes of rectal hemorrhage every 2 years for 14 years, but none as severe as this. Previous investigations had failed to reveal the site of bleeding. He showed incipient signs of shock on admission with 8.2 Gm. of hemoglobin but improved with multiple blood transfusions. He continued to bleed rectally, and on the sixth hospital day he suddenly went into profound shock. Again multiple transfusions were required to restore his blood pressure to normal levels. Because of continued massive rectal bleeding, an emergency exploratory laparotomy was performed. A large dilated colon was encountered which was filled with dark blood and contained hundreds of diverticula scattered throughout its entire length. These diverticula were distended with blood. There was no blood in the remainder of the gastrointestinal tract and no other source of bleeding was found. These multiple diverticula were thought to be the source of the hemorrhage, and because of the intensity of the bleeding some definitive procedure seemed advisable. Resection seemed contraindicated because of the patient's poor general condition, so a proximal ascending colostomy was made. The colon was divided and its stomas were placed in the ends of a right rectus incision. The bleeding promptly stopped and at no time were bloody or tarry stools passed from the proximal colostomy. Convalescence was uneventful. Three weeks later, after suitable preparation, subtotal colectomy was performed resecting the cecum and ascending colon including the colostomy, the transverse and descending colons, and most of the sigmoid colon. An ileosigmoidostomy was done to restore gastrointestinal continuity. Recovery following this procedure was without complication. Since that time, the patient has had 1 to 3 bowel movements each day and these vary from solid to semisolid in consistency. There has been no bleeding since the initial operation.

Second Series.—From 1949 through 1955, 104 patients were admitted to the Confederate Memorial Medical Center with a proved diagnosis of diverticulosis and/or diverticulitis. Thirty-three patients gave a history of gross bleeding from the rectum, presumably due to diverticular disease of the colon. This is an incidence of 31.7 per cent. Complete evaluation of those 33 patients showed no other cause for rectal bleeding. The diagnosis of diverticulosis was established by colon x-ray in these patients and 10 showed disease involving almost the entire colon. Proctoscopic examination of one patient showed bleeding from the mouth of a diverticulum in the sigmoid colon. Seven patients of the 33 with rectal bleeding were considered to have massive bleeding

TABLE II. DATA ON PATIENTS WITH SEVERE HEMORRHAGE FROM DIVERTICULOSIS (Confederate Memorial Medical Center 1949-1955)

PATIENT	AGE	SYMPTOMS	REMARKS	OUTCOME
1. L. F.	68	3 days of rectal bleeding with marked weakness; similar episode 3 or 4 months before	5.8 Gm. hemoglobin on admission; required 9 pints of blood and bleeding stopped after 3 or 4 days; x-ray showed diverticulosis of colon from hepatic flexure to rectum; remainder work-up including gastrointestinal x-rays normal	Lived
2. L. S.	73	Sudden onset rectal hemorrhage; approximately 1 pint red blood; similar episode 5 years before	9.2 Gm. hemoglobin and mild shock on admission; required multiple transfusions but hemorrhage stopped promptly; x-rays showed diverticulosis of entire colon; other studies normal	Lived
3. R. E.	56	4 days of dark red to black stools	X-ray showed multiple diverticula throughout colon; remainder gastrointestinal studies normal; no evidence of other etiology of hemorrhage; received multiple transfusions and bleeding ceased	Lived; has occasional rectal bleeding but controlled with low residue diet
4. W. D.	67	4 days of tarry stools mixed with red blood	9.9 Gm. hemoglobin; no evidence of shock; required multiple transfusions and bleeding ceased; x-ray showed many diverticula from hepatic flexure through the sigmoid colon; remainder gastrointestinal x-rays negative	Lived; similar hemorrhage 2 years later but not severe; responded to conservative measures
5. E. F.	68	48 hours of diarrhea with tarry stools mixed with red blood	Hemoglobin 5.5 Gm. on admission; no shock; required 6 pints of blood as transfusion and stopped bleeding; x-ray studies of gastrointestinal tract negative except for diverticulosis of the colon, predominantly of sigmoid; patient was operated upon with plan to resect sigmoid, but exploration revealed massive diverticulosis of entire colon so no resection was carried out	Lived
6. S. P.	75	2-year history of rectal bleeding; recent episode 5 days before admission; passed approximately 1 quart of blood; fainted	Hemoglobin 7.5 Gm.; transfused with 4 pints blood; recovered and 3 months later similar episode with hemoglobin of 8 Gm.; required 6 pints blood; developed homologous serum jaundice; 4 years later another massive hemorrhage; required 7 pints blood; repeated x-ray studies showed only diverticulosis of entire colon	Subsequently died from uremia accompanying staghorn calculus in solitary kidney; autopsy showed extensive diverticulosis entire colon; no other source of hemorrhage found
7. W. T.	67	Profuse hemorrhage from rectum; red blood; similar episode 3 years before	Hemoglobin 8.5 Gm.; no evidence of shock; bleeding stopped after 2 transfusions; proctoscopy—mouth of diverticulum seen containing blood; x-ray—diverticula of hepatic flexure, splenic flexure, descending and sigmoid colons; remainder studies negative	Lived

in that they showed evidence of shock and/or marked blood loss and/or required 1,000 c.c. or more of whole blood as replacement therapy. Summarizing data concerning these 7 patients are found in Table II. Four of these 7 patients had diverticulosis of the entire colon while the other 3 had diverticula present from the hepatic flexure to the rectum. All these patients lived except one who died of uremia associated with stones in a solitary kidney. Autopsy on this patient showed no cause of gastrointestinal bleeding except extensive diverticulosis.

One patient of this group (Table II, E. F.) was operated upon, and this was an elective operation after massive bleeding had stopped. Preoperative studies revealed diverticula of the sigmoid and resection of the sigmoid was planned. Exploration revealed massive diverticulosis of the entire colon so no further surgery was performed. There has been no further bleeding.

One patient has been treated at the Confederate Memorial Medical Center for massive bleeding this year and is not included in the above series. Because of the therapeutic problem encountered, a brief abstract of the patient's history and course is presented.

L. N., an 82-year-old Negress, was admitted to the hospital on May 15, 1956, complaining of passing a large quantity of red blood rectally 6 hours before admission. There was no history of hematemesis or of similar rectal bleeding in the past. Clinical study revealed a marked anemia but proctoscopic examination, upper gastrointestinal x-rays, liver function studies, and bleeding and clotting times were reported as normal. Rectal bleeding continued and multiple blood transfusions were necessary for replacement. Four days after admission she went into profound shock, and after additional transfusions emergency laparotomy was performed. Exploration revealed the entire colon to be distended with blood with numerous diverticula present throughout the left colon. Jejunal diverticula were also present but there was no blood in the small intestine. Multiple colotomies showed the blood in the right colon to be old while there was fresh blood in the left colon. The patient's age and general condition seemed to contraindicate colon resection so a midtransverse colostomy was made. The patient's bleeding stopped and although her postoperative course was a stormy one including an episode of acute heart failure, she responded to treatment and made a satisfactory recovery. Since her discharge from the hospital she has had no further gastrointestinal bleeding.

DISCUSSION

The incidence of gross bleeding in patients with diverticular disease of the colon shows great variation in reported series. Noer[7] collected 28 series and found a range of 3 to 47 per cent. There is no explanation offered for the differences encountered. There was also considerable discrepancy noted in the two series herein reported (12.4 per cent compared to 31.7 per cent). The smaller incidence here occurred in the private hospital series and the larger one in a large charity institution where pathologic processes are generally more advanced before admission. Whether this is a factor in the difference is a matter for conjecture.

It is difficult to estimate the incidence of massive hemorrhage in this disease. In 1954, Noer[7] collected 41 cases of severe bleeding reported since 1942 and added 7 cases of patients in whom bleeding was sufficient to require operation. Other authors[2, 4, 5, 8, 10, 12, 16, 17] have reported additional cases of massive hemorrhage from diverticulosis but this complication still occurs infrequently. Fifteen patients in the two series herein reported had sufficient

hemorrhage to require multiple transfusions and were considered to have severe bleeding. These patients' records were studied carefully to ascertain any common denominator which might set them apart from the other patients with diverticulosis or diverticulitis, who had no bleeding or bled only slightly.

One is impressed on reviewing our cases that severity of bleeding seemed to be correlated with extent of diverticular involvement of the colon. Of the 15 reported cases of severe bleeding, 7 had involvement of the entire colon, and 4 others had involvement of most of the colon extending from the hepatic flexure through the sigmoid colon. Only 4 who had localized colonic involvement bled massively. There was only an occasional case in this series of diverticula involving the entire colon in which, if bleeding had occurred, it was not severe.

Other reports give some support to the thesis that severity of bleeding may be a function of the extent of diverticular disease. Some authors have not been specific in regard to the extent of the diverticulosis but others indicate that massive bleeding was frequently associated with extensive diverticulosis. The patient who required emergency subtotal colectomy reported by Cate[1] had diverticulosis of the entire colon, and the only patient with severe hemorrhage reported by Neal[6] was one with extensive diverticulosis. Young and Howorth's[17] patient with massive hemorrhage also had diverticular involvement of most of the colon. Thompson[14] encountered 2 patients with severe hemorrhage from diverticulosis, and he noted one had diverticulosis of the entire colon while the extent of disease in the second case was not specified. Noer[7] reported 2 cases of hemorrhage severe enough to require emergency surgery, and one of these had involvement of the entire colon. Chenoweth[2] cites a similar experience with 2 patients requiring emergency surgery, one of whom had diverticulosis from the cecum to the rectosigmoid. In Quinn and Ochsner's series[8] the only patient who was operated upon as an emergency was one with diverticulosis of the entire colon. Welch and his colleagues[16] reported 3 cases of massive bleeding, one of which had extensive diverticulosis.

In view of these cases, the observation seems justified that exsanguinating hemorrhage from diverticulosis is most likely to occur when the pathologic process involves the colon extensively. However, severe bleeding from localized diverticulosis can occur, and reports[4, 5] indicate that it may also be extremely hazardous to the patient.

There is no implication here that all patients with extensive diverticulosis bleed massively. As previously noted, massive bleeding is a rare occurrence, while the reports of Sanders[11] and Val Dez and his associates[15] indicate that diverticulosis of the entire colon is more common than generally appreciated. A combination of their reports reveals only 4 patients with massive bleeding although 128 patients had extensive diverticulosis.

The exact mechanism of hemorrhage in patients with diverticular disease of the colon remains obscure although clinical and pathologic observations[7, 17] have been made which may help in its clarification. Attention has been called to the fact that diverticulosis seems more likely to produce massive hemorrhage

than diverticulitis and that infection is not essential for bleeding to occur.[9, 10] A lack of association of bleeding and inflammation was also noted in this series. No patient with severe bleeding had signs and symptoms of diverticulitis at the time of hemorrhage or a suggestive history in the past. If associated inflammation cannot be incriminated, local trauma producing ulceration with subsequent hemorrhage may be the most important etiologic factor in hemorrhage in this disease.

TREATMENT

Due to the infrequency of massive hemorrhage in diverticular disease of the colon, treatment has not been well standardized. Since the majority of bleeding is mild, a plan of conservative therapy usually will suffice. This should include rest, sedation, and transfusions as indicated with subsequent instructions concerning a bland diet and avoiding constipation. This has been the therapeutic approach by most clinicians, and the results[6, 8, 14] have been good. When the bleeding is recurrent or severe and the disease process is proved to be localized, it seems justified to perform an elective resection of the diseased bowel. Reported results[3, 7, 8, 12] indicate that this also has been a satisfactory procedure.

Even with the occurrence of massive hemorrhage from colonic diverticula, the conservative regime is the treatment of choice. Most of these patients will stop bleeding if their blood loss is carefully replaced and they are observed over a period of time. The success of this type of program is well illustrated by Patient B. M. in Table I whose numerous, recurrent, severe hemorrhages have always responded to conservative therapy. One should note, however, reports[8, 14] of patients with diverticulosis who exsanguinated on a conservative program of treatment. These attest to the fact that such a plan is not always successful and should not be followed indefinitely.

The real therapeutic challenge comes when these massively bleeding patients do not stop bleeding and emergency laparotomy is performed to prevent the patient from exsanguinating. In this situation, if the patient has a segmental disease process, resection can be carried out and the bleeding stopped. This procedure has been utilized by a number of surgeons and some of the reported results[2, 5] have been good. When the patient is bleeding massively from extensive diverticulosis involving the entire colon, the best choice of a surgical procedure is not so clear. One may elect to close the abdomen under these circumstances and hope that the bleeding will stop. While some of these patients may stop bleeding, reports by Cate[1] and Quinn and Ochsner[8] of their experiences with such a choice do not lend support to such optimism. These authors reported patients who continued to bleed after closure and subsequently required a second laparotomy and more definitive surgery.

The second plan of treatment a surgeon has available, with the abdomen open and a patient bleeding from extensive diverticulosis, is emergency resection of the diseased bowel or the bleeding area if the site of hemorrhage can be localized. Unfortunately the localization of the precise bleeding point is usually impossible. In properly selected cases, a resection of most of the

colon is feasible and may be dramatically successful as in the case reported by Cate.[1] One must not forget, however, that subtotal colectomy may be a formidable procedure, especially when carried out as an emergency for exsanguinating hemorrhage. Quinn and Ochsner[8] and Young and Howorth[17] reported patients similar to Cate's who died following emergency total colectomy for hemorrhage from extensive diverticulosis. Noer[7] has emphasized the increased hazard of emergency resections in these patients. Seven patients required resection in his series, and the 3 who required emergency surgery all died. Hoar and Bernhard[4] also reported fatalities in 3 of 4 patients following emergency operations for massive bleeding diverticula although the resections were more limited.

The surgeon may attempt to guess which half of the colon is responsible for the majority of the bleeding and resect only this portion. A survey of the literature, however, suggests that with extensive diverticulosis, limited resections may be followed by continued bleeding and require resection of more colon to control it. Welch and his colleagues[16] report a patient who had sigmoid resection for massive bleeding but in whom a second hemorrhage from extensive diverticulosis necessitated total colectomy. Noer[7] reported a patient who had an emergency right hemicolectomy for massive bleeding from diverticulosis followed by further hemorrhage necessitating total colectomy.

In the cases reported here, we have been impressed with the fact that these patients would not tolerate extensive resection as an emergency and have elected to do a less formidable procedure and divert the fecal stream by means of a colostomy. In our first patient (E. M., Table I) a colostomy was made in the ascending colon, thus diverting the fecal stream from almost all the colon. This procedure was chosen over an ileostomy which is frequently poorly tolerated by patients. In our second patient, a transverse colostomy was elected because it was believed that the bleeding was from the left colon since all the diverticula were located on the left. The results in these 2 cases, as described in the case reports, were good. Chenoweth[2] has also utilized diversion of the fecal stream to stop massive hemorrhage from diverticulosis. In his reported case ileostomy was performed with an immediate good result.

It is difficult to evaluate results of therapy for bleeding in diverticulosis as in other disease processes because a number of patients will stop bleeding regardless of type of treatment. The results of colostomy herein reported are few in number but have been sufficiently dramatic to suggest that colostomy may be the safest way to stop severe bleeding in extensive diverticulosis. If subsequent experience confirms the fact that bleeding from the right colon seldom occurs, transverse colostomy might suffice in all cases.

If colostomy is performed and bleeding is controlled, the proper course for subsequent therapy probably will require individualization. Our first patient had a subsequent subtotal colectomy as an elective procedure, and he has had no further difficulty. Our second patient still has her colostomy and due to

her age and general condition will probably be allowed to keep it. Chenoweth's[2] patient had considerable difficulty with his ileostomy, and the ileostomy was subsequently closed and he has had no further bleeding. It seems that, if there are no extenuating circumstances, patients who have required an emergency procedure for hemorrhage should have an elective resection at a later date.

SUMMARY

Hemorrhage as a complication of diverticular disease of the colon has been studied in 2 series of patients and the results are reviewed.

Massive hemorrhage was noted in 14 patients and these constituted 4.8 per cent of the combined series of 289 patients. Of these 14 patients, 7 had diverticular involvement of the entire colon and 4 others had involvement extending from the hepatic flexure to the rectum. This and data from other reported series suggest that exsanguinating hemorrhage is most likely to occur when the colon is extensively involved by diverticular disease.

In so far as could be determined, inflammation was not a factor in the massive hemorrhage encountered because none of these patients had signs or symptoms of diverticulitis.

The treatment of hemorrhage complicating colonic diverticulosis is outlined, and the problem of the severe bleeder who does not respond to conservative measures is considered. Two case reports are presented to illustrate use of colostomy to stop hemorrhage in diverticular disease. It is suggested that simple diversion of the fecal stream may be the safest way to control massive hemorrhage from diverticulosis.

REFERENCES

1. Cate, W. R., Jr.: Colectomy in the Treatment of Massive Melena Secondary to Diverticulosis, Ann. Surg. **137**: 558, 1953.
2. Chenoweth, A. I.: Discussion of paper by R. J. Noer, Ann. Surg. **141**: 684, 1955.
3. Fallis, L. S., and Marshall, M. R.: Acute Diverticulitis of the Large Bowel, Am. J. Surg. **80**: 198, 1950.
4. Hoar, C. S., and Bernhard, W. F.: Colonic Bleeding and Diverticular Disease of the Colon, Surg., Gynec. & Obst. **99**: 101, 1954.
5. McCutcheon, G. T.: Discussion of paper by R. J. Noer, Ann. Surg. **141**: 684, 1955.
6. Neal, J. W.: Diverticulitis of the Colon and Its Surgical Management, SURGERY **30**: 606, 1951.
7. Noer, R. J.: Hemorrhage as a Complication of Diverticulitis, Ann. Surg. **141**: 674, 1955.
8. Quinn, W. C., and Ochsner, A.: Bleeding as a Complication of Diverticulosis or Diverticulitis of the Colon, Am. Surg. **19**: 397, 1953.
9. Rives, J. D.: Discussion of paper by R. J. Noer, Ann. Surg. **141**: 685, 1955.
10. Rosser, C.: Discussion of paper by R. J. Noer, Ann. Surg. **141**: 683, 1955.
11. Sanders, L. C.: Diverticulitis of the Colon, Rev. Gastroenterol. **13**: 294, 1953.
12. Starkloff, G. B., and Lewis, J. E., Jr.: The Surgical Treatment of Sigmoid Diverticulitis, Am. Surg. **22**: 295, 1956.
13. Stone, H. B.: Melena of Obscure Origin, Ann. Surg. **120**: 582, 1944.
14. Thompson, J. W.: Acute Sigmoid Diverticulitis, J. Internat. Coll. Surgeons **17**: 52, 1952.
15. Val Dez, F. C., Gilbert, C. S., and Kash, W.: Colonic Diverticula: A Review of 234 Cases, Illinois M. J. **93**: 269, 1948.
16. Welch, C. E., Allen, A. W., and Donaldson, G. A.: An Appraisal of Resection of the Colon for Diverticulosis of the Sigmoid, Ann. Surg. **139**: 332, 1953.
17. Young, J. M., and Howorth, M. B., Jr.: Massive Hemorrhage in Diverticulosis: Possible Explanation of Cause With Presentation of Case Requiring Surgical Treatment, Ann. Surg. **140**: 128, 1954.

RESPIRATORY DEPRESSION DUE TO NEOMYCIN

HAROLD L. ENGEL, M.D., AND J. S. DENSON, M.D., LOS ANGELES, CALIF.

(From the Section of Anesthesia, University of Southern California School of Medicine, and the Departments of Anesthesia, the College of Medical Evangelists, and the Los Angeles County Hospital)

THE antibiotic neomycin has been used extensively in intestinal surgery to prepare the bowel preoperatively and to treat peritonitis encountered during exploratory laparotomy. Pridgen[1] has recently reported 4 cases in which the instillation of neomycin into the peritoneal cavity was followed by respiratory arrest.

At the Los Angeles County Hospital neomycin is used intraperitoneally in almost every case in which a perforation of the gastro-intestinal tract is present. The drug is instilled in 1 or 2 Gm. doses in from 20 to 300 c.c. of saline just prior to closing the peritoneum. No correlation between this procedure and respiratory difficulties was suspected until the article by Pridgen suggested a review of our cases.

All of the surgical cases, whether neomycin was used or not, in which serious respiratory difficulties developed during surgery or immediately postoperatively from July, 1953, to January, 1957, were reviewed. A total of 225 cases out of 47,000 operations fell into this category. In 4 of these, all small children, respiratory depression occurred about 15 minutes after the instillation of the neomycin. No muscle relaxant (such as curare or succinylcholine) was used during the procedures. Each patient's respiration had been quite adequate prior to the use of neomycin.

CASE REPORTS

CASE 1.—A 3-year-old girl who had had abdominal pain and vomiting for 2 days was brought to the operating room for an appendectomy. The rectal temperature was 104° F.; pulse rate 140; respirations 36; blood pressure 100/70; hemoglobin 10.0 Gm.; and white blood cell count 19,750. Preanesthetic medication of atropine, gr. 1/350, was administered intramuscularly 30 minutes prior to surgery. Anesthesia was induced with open drop Vinethene and maintained with open drop ether, with 300 c.c. of oxygen per minute insufflated under the mask. The respiratory rate after induction was 40 per minute. Free pus was found in the abdomen and a suppurating appendix was removed. Just prior to closing the abdomen one gram of neomycin in 350 c.c. of saline was introduced into the peritoneal cavity. Surgery lasted one hour. The anesthesiologist's notes read: "Patient breathing well throughout. At about the last skin stitch she suddenly stopped breathing although she was moving her hands. A marked bradycardia developed. The trachea was intubated and controlled breathing with oxygen begun." After 45 minutes of artificial ventilation, spontaneous respiration began to return but was not considered adequate for another hour. The child made an uneventful recovery.

Received for publication Feb. 25, 1957.

CASE 2.—A one-month-old boy was admitted to the hospital with fever and diarrhea. These symptoms subsided only to be followed by abdominal distention. A diagnosis of small bowel obstruction was made and an exploratory laparotomy scheduled. Temperature 98.6° F.; pulse rate 140; respirations 32; hemoglobin 12 Gm.; white blood cell count 10,800. Preanesthetic medication of scopolamine, gr. 1/400, was administered intramuscularly 30 minutes prior to anesthesia. An orotracheal intubation was accomplished while the baby was awake and anesthesia was induced and maintained with nitrous oxide-oxygen-ether using a nonrebreathing technique. Respiratory rate varied from 40 to 70 per minute throughout the procedure. A reduplication of the terminal ileum with many perforations and marked spillage of intestinal contents was found. The terminal ileum was resected and an end-to-end anastomosis and appendectomy performed. One gram of neomycin was introduced into the peritoneal cavity just prior to its closure. The duration of surgery was 2½ hours. Ten minutes after the endotracheal airway was removed, about 20 minutes after the neomycin was used, the baby suddenly stopped breathing. His trachea was immediately reintubated and artificial ventilation instituted. In another 20 minutes spontaneous respiration began to return. Ten minutes later respiration was considered adequate and the endotracheal airway was again removed. Respiration was described as "jerky" for 4 hours postoperatively following which it became normal. The baby was progressing well following surgery but died unexpectedly on the eleventh postoperative day. Permission for autopsy was denied.

CASE 3.—A 21-month-old boy who had had abdominal pain and vomiting for 40 hours was brought to the operating room for an appendectomy after having received scopolamine, gr. 1/600. Temperature was 102.2° F.; hemoglobin 9 Gm.; white blood cell count 17,000. He was placed on an ice water mattress and anesthesia was induced with cyclopropane and oxygen. An orotracheal airway was placed in position and anesthesia was maintained with nitrous oxide-oxygen-ether. A nonrebreathing technique was used. Throughout the operation the pulse rate remained around 130 per minute, the blood pressure at 90/60, and the respiratory rate at 40 per minute. Generalized peritonitis was found and a ruptured appendix was removed. One gram of neomycin was instilled into the peritoneal cavity just prior to its closure. The surgery required 45 minutes. The patient became apneic about 10 minutes after the use of neomycin although the level of anesthesia was quite light. Following 40 minutes of artificial ventilation with oxygen, spontaneous respiration returned and in 20 minutes was adequate. The baby made an uneventful recovery.

CASE 4.—A 4-pound infant was 12 hours old when brought to the operating room for an abdominal exploration because of marked distention. Temperature was 96.6° F.; pulse rate 140; respiration 40; and hemoglobin 14 Gm. Preanesthetic medication of atropine, gr. 1/500, had been administered. An orotracheal intubation was completed while the baby was awake and anesthesia was induced and maintained with cyclopropane and oxygen. A T-tube technique was utilized. A gangrenous, perforated small bowel was found. The diseased section of bowel was resected and a small bowel-cecal anastomosis performed. Neomycin (quantity unknown) was instilled into the peritoneal cavity prior to its closure. At this time the cyclopropane was discontinued and only oxygen administered. The baby breathed well for 30 minutes but then respiration almost completely disappeared. In spite of artificial ventilation with oxygen for 2 hours the baby died.

CONCLUSION

In addition to these 4 cases, 19 others have been found in which respiratory depression or apnea developed after the use of intraperitoneal neomycin. However, in each of these cases a muscle relaxant had been used so that it was difficult to determine whether one of the drugs or both was responsible. In 4 of these 19 cases, the dose of relaxant used, the nature of the respiration following

its use, and the development of respiratory difficulty 15 to 30 minutes following the use of neomycin would tend to point to the antibiotic rather than the relaxant as the cause of trouble.

The cases reported in this article do not provide conclusive proof that intraperitoneal instillation of neomycin can produce apnea in anesthetized patients. It must be emphasized that neomycin has been used in this manner in hundreds of cases without observed effect on respiration. These cases do seem to indicate, however, that in some instances, particularly in small children and critically ill adults, neomycin may produce severe respiratory depression.

REFERENCE

1. Pridgen, James E.: Respiratory Arrest Thought to Be Due to Intraperitoneal Neomycin, SURGERY 40: 571-574, 1956.

THIOSTREPTON AND THIOSTREPTON-NEOMYCIN FOR PREOPERATIVE PREPARATION OF THE COLON

ISIDORE COHN, JR., M.D., AND ALFRED B. LONGACRE, M.D., NEW ORLEANS, LA.

(From the Department of Surgery, Louisiana State University School of Medicine)

SINCE an ideal agent has not yet been found for preoperative preparation of the colon, it has seemed worthwhile to continue to evaluate new agents to determine whether or not they would be effective for this purpose. Thiostrepton, obtained from an unidentified strain of *Streptomyces* isolated from a New Mexico soil sample, has been described as a new antibiotic which is not absorbed from the gastrointestinal tract and which has in vivo activity against micrococci.[9-11] These factors stimulated interest in this drug for preoperative intestinal antisepsis.

METHODS

Patients were chosen at random from the surgical service, provided they were in good general condition and had no known colonic lesions.* During the period of study they received only those antibacterial agents administered for intestinal antisepsis. The patients were not subjected to surgery during the period of investigation.

After a control stool was obtained the patients were placed on a program similar to that for patients being prepared for large bowel surgery. A low residue diet, a laxative the first day of therapy, and daily enemas thereafter added mechanical cleansing to the program for reduction of the bacterial flora of the colon.

Bacteriologic analyses were conducted on stools collected before therapy, each day during therapy, and for one to two days after therapy. Drug sensitivity of the organisms recovered in the stool each day was evaluated.

Bacteriologic techniques were identical with those used in previous studies.[3-5] Briefly these consisted of serial dilution of a weighed quantity of stool and aerobic and anaerobic plating of each dilution so as to obtain 15 initial plates from each stool specimen. Colony counts were made at appropriate intervals and organisms identified through Gram's stain smears and subcultures as necessary. Additional subcultures or additional tests were performed when necessary. Identification of the various organisms followed the same techniques reported in previous studies.

Aided in part by Research Grant No. E-524-(C3) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service, and by a grant from the E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corporation, New York, N. Y.

Thiostrepton was supplied by The Squibb Institute for Medical Research as M-3339.

Bacteriologic determinations were conducted by Bette M. Beauclair, B. S., and Esther C. Alexander, B.S.

Received for publication March 15, 1957.

*Louisiana State University Surgical Service of the Charity Hospital of Louisiana at New Orleans.

Discs containing various concentrations of the drug were used for sensitivity studies.

THIOSTREPTON

Thiostrepton was administered every 6 hours for 72 hours in an oral dose of 500,000 units. Five patients were studied (Fig. 1).

Streptococci were present in all control specimens. They were absent from one patient by the end of the first day of therapy and continued to be absent in this patient throughout therapy. In one patient streptococci disappeared on the day after therapy but were not controlled during therapy. In another patient streptococci disappeared transiently during therapy but reappeared. In the remaining 2 patients streptococci were not significantly affected.

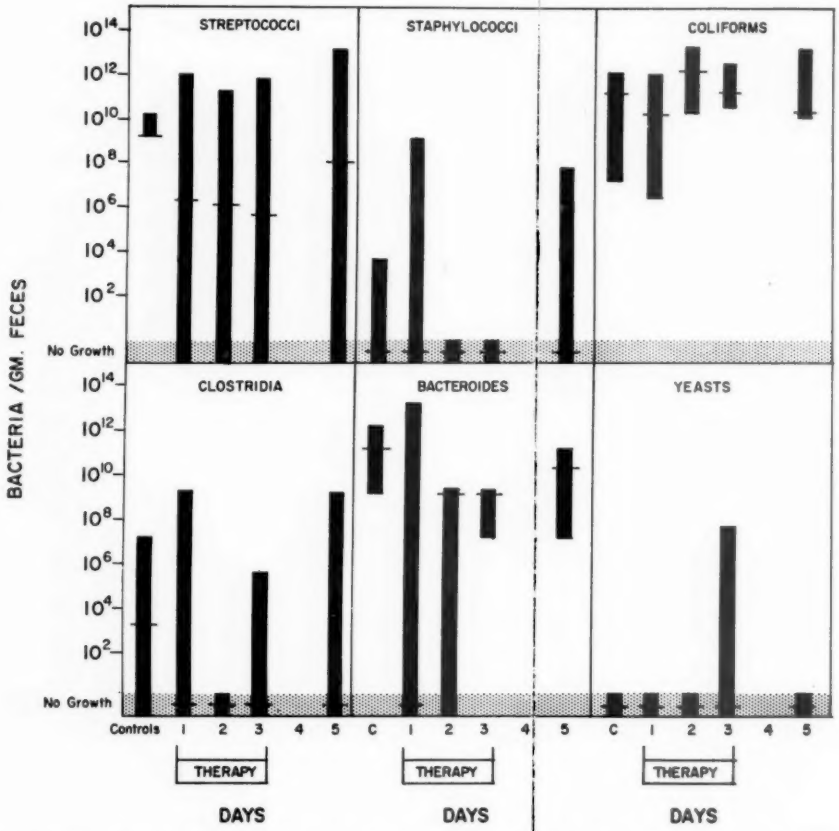


Fig. 1.—Effect of thiostrepton given for 3 days on bacteria in feces. Bars indicate maximum and minimum values for each day. Cross marks indicate median value.

Staphylococci were present in only one control specimen and appeared on the first day of therapy in one additional patient. They were not found at any other time during therapy in any of the other patients.

Coliform organisms were present in all control specimens and continued to be present in undiminished concentration throughout therapy and the immediate posttherapy period.

Clostridia were present in 3 control specimens but were not subsequently found in 2 of these patients. They were not controlled in the third patient. In one patient clostridia appeared for the first time after therapy.

Bacteroides were present in all control specimens and were present in all patients in essentially unchanged concentration at the end of therapy.

Yeasts appeared only once at the end of therapy in one patient.

In addition to these organisms, aerobic Gram-positive rods were found in 3 patients, proteus species were found in 3 patients, and pseudomonas species were found in one patient.

Sensitivity studies were conducted using discs containing 5 and 50 mcg. of thiostrepton (Table I).

TABLE I. SENSITIVITY STUDIES ON ORGANISMS RECOVERED BEFORE AND AFTER THIOSTREPTON THERAPY

	STREPTOCOCCI		STAPHYLOCOCCI		COLIFORMS		CLOSTRIDIA		BACTEROIDS	
PATIENT	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
Fon	S^{5}	S^{50}	NG	NG	R	R	S^{5}	NG	R	R
Joh	S^{50}	NG	R	R	R	R	NG	R	R	R
Mid	S^{50}	S^{50}	NG	NG	R	R	S^{5}	NG	R	R
Mor	S^{50}	S^{5}	NG	NG	R	R	NG	NG	R	R
Wil	S^{50}	NS	NG	NS	R	NS	S^{5}	NS	R	NS

S^{5-50}—Sensitive to 5 or 50 mcg. of drug.
R—Resistant to drug activity.
NG—No growth.
NS—No specimen.

All streptococci in the control specimens were sensitive to one or the other concentration of the drug. No organisms became resistant during therapy, but in one patient the streptococci were initially sensitive to 5 mcg. and became sensitive to 50 mcg. after a single day of therapy.

Since staphylococci were found so infrequently, their sensitivity cannot be evaluated here. In the one patient in whom staphylococci appeared before and after therapy, they were resistant at both times even though they seemed to have been controlled during therapy. Staphylococci which appeared only on the first day of therapy in one patient were sensitive to the lower level of thiostrepton.

All coliform organisms evaluated were resistant to the drug.

Clostridia found throughout the study were sensitive to 5 micrograms of thiostrepton.

All bacteroides studied were resistant to the drug and this coincides with their lack of control.

Thus there was no significant change in the sensitivity of streptococci, while coliform organisms and bacteroides remained resistant throughout therapy.

THIOSTREPTON-NEOMYCIN

Thiostrepton-neomycin was administered as follows: thiostrepton 500,000 units every 6 hours for 72 hours, neomycin one gram every hour for 4 hours, then one gram every 6 hours for 72 hours. Seven patients were studied.

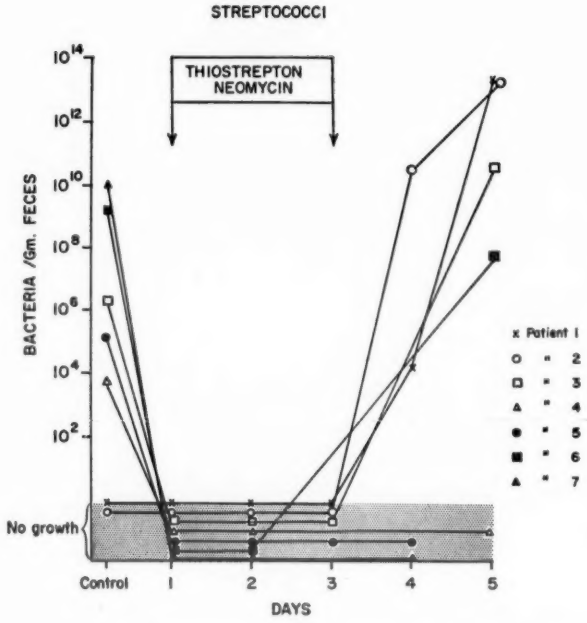


Fig. 2.—Streptococci per gram of stool in patients on thiostrepton-neomycin for 3 days. Each symbol represents one patient. Symbols are plotted only for days when specimens obtained and analyzed. Symbols in area of "No Growth" indicate specimens analyzed and found free of these organisms.

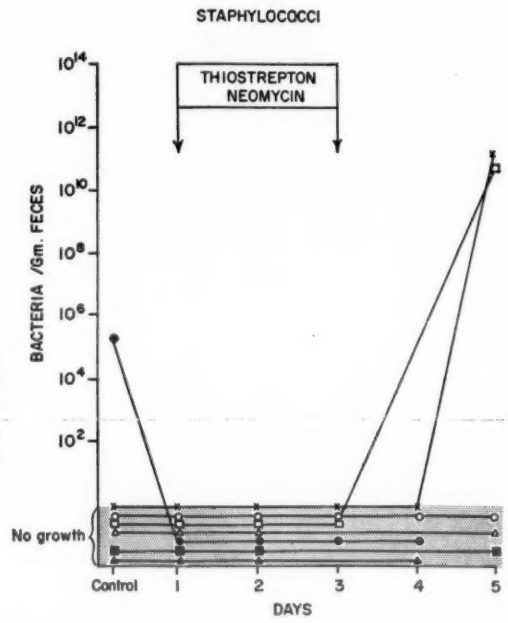


Fig. 3.—Staphylococci in feces during and after thiostrepton-neomycin therapy.

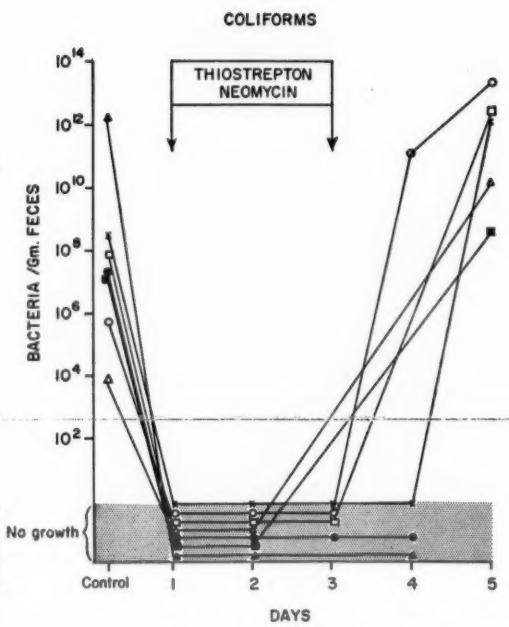


Fig. 4.—Coliform organisms in same patients during and after thiostrepton-neomycin therapy.

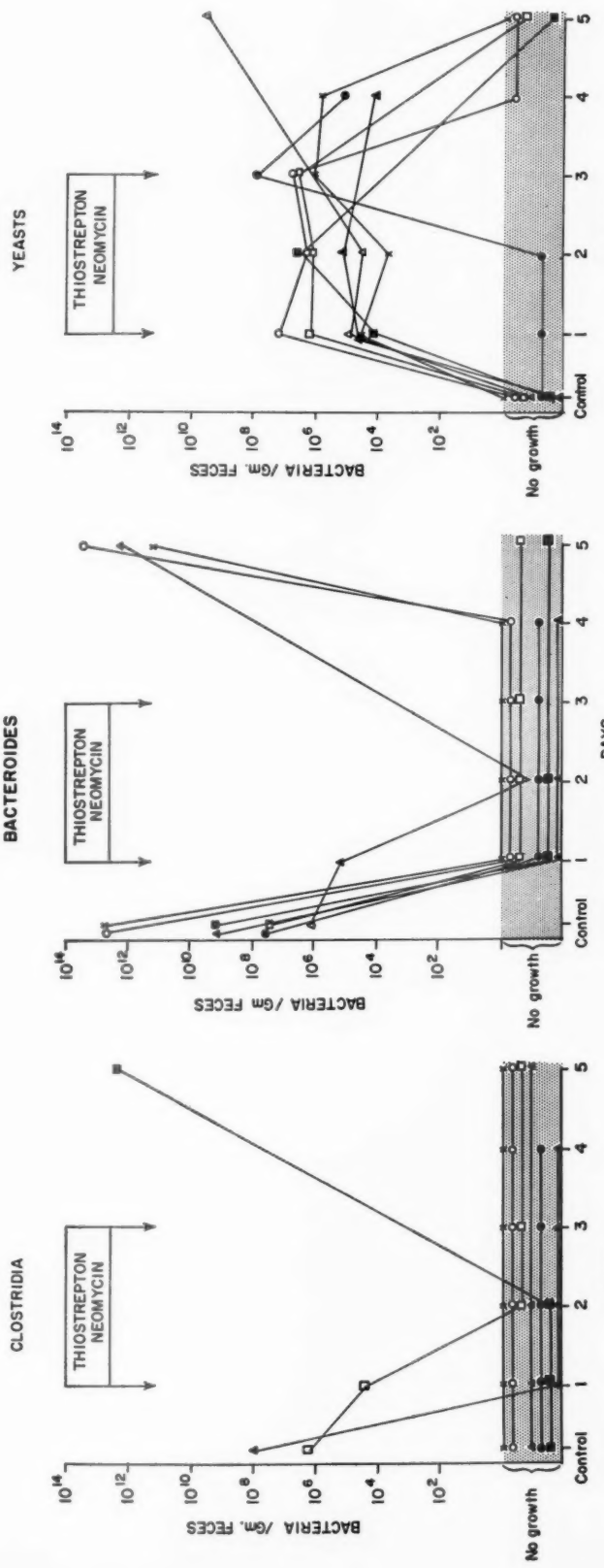


Fig. 5.—Clostridia in stool during and after thiostrepton-neomycin therapy.

Fig. 6.—Effect of thiostrepton-neomycin therapy on bacteroides in feces.

Fig. 7.—Effect of thiostrepton-neomycin therapy on yeasts in same patients.

TABLE II. SENSITIVITY STUDIES ON ORGANISMS RECOVERED BEFORE AND AFTER THIOSTREPTON-NEOMYCIN THERAPY

PATIENT	STREPTOCOCCI				STAPHYLOCOCCI				COLIFORMS				CLOSTRIDIA				BACTEROIDES			
	BEFORE		AFTER		BEFORE		AFTER		BEFORE		AFTER		BEFORE		AFTER		BEFORE		AFTER	
	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN	THIOSTREPTON	NEOMYCIN
Bab	NG	NG	R	R	NG	NG	R	S5	R	S5	R	S5	NG	NG	NG	NG	R	R	R	R
Ber	NG	NG	R	R	NG	NG	NG	NG	R	S5	R	S5	NG	NG	NG	NG	R	R	R	R
Cro	S5	R	R	S50	NG	NG	S50	R	R	S5	R	S5	S5	R	NG	NG	R	R	S50	R
Fer	S50	S50	S50	S5	NG	NG	NG	NG	R	S5	R	S5	NG	NG	NG	NG	R	R	R	R
Lan	S50	R	NG	NG	NG	R	NG	NG	R	S5	NG	NG	NG	NG	NG	NG	R	R	NG	NG
Lea	*	*	S5	R	S5	NG	R	S5	R	S5	R	S5	NG	NG	S5	R	S5	S5	NG	NG
Smi	S5	R	NG	NG	NG	NG	NG	NG	R	S5	NG	NG	S5	R	NG	NG	S5	S50	NG	NG

*Sensitivity studies not conducted.
S^{5-50}—Sensitive to 5 or 50 mcg. of drug.
R—Resistant to drug activity.
NG—No growth.

Other studies have shown that neomycin alone gives better control of the bacterial flora of the colon than any other agent used by itself.[4-6] However, control is not complete with neomycin, and when neomycin has been combined with a number of other agents a synergistic-like effect has been observed repeatedly.[1-8]

Streptococci were present in 5 control specimens but were not subsequently found during therapy in any of the patients (Fig. 2). Streptococci appeared for the first time on the day after therapy in the 2 patients that had previously been free of streptococci and appeared on the second day after therapy was discontinued in 2 additional patients.

Staphylococci were present in only one control specimen and were not subsequently found during the period of therapy in any of the patients (Fig. 3). Staphylococci first appeared on the second day after therapy in 2 patients.

Coliform organisms were present in all control specimens but were not subsequently found during the period of therapy in any of the patients (Fig. 4). They reappeared on the first day after therapy in one patient and reappeared on the second day after therapy in 4 additional patients.

Clostridia were found in 2 control specimens and on the first day of therapy in one of these patients (Fig. 5). They were not otherwise found during therapy.

Bacteroides were found in all control specimens and on the first day of therapy in one patient (Fig. 6). They were not otherwise found during therapy or on the first day after therapy in any patient. Bacteroides did appear on the second day after therapy in 3 patients.

Yeasts were not found in any control specimens but appeared on the first day of therapy in 6 patients and by the end of therapy had been found in all of the patients under study (Fig. 7). There was a further slight increase in the count of yeasts during therapy. Yeasts were not cultured on the second day after therapy in 5 patients indicating the rapid return to a normal bacterial flora.

In addition to the organisms already discussed, proteus species were found in 2 patients, and aerobic Gram-positive rods and pseudomonas species were each found in one patient.

Sensitivity studies were conducted using discs containing 5 and 50 mcg. of each of the drugs alone (Table II) and in combination in both concentrations on a single disc. The results are only reported for the drugs separately since these and previous studies[7, 8] have indicated that the results obtained using the 2 agents separately were identical with those using the 2 agents together.

All streptococci in the control specimens were sensitive to thiostrepton, but 3 of the 4 patients had streptococci which were resistant to neomycin. The streptococci which appeared for the first time after therapy in 2 patients were resistant to both drugs. In one other patient, the streptococci which appeared afer therapy were resistant to thiostrepton and sensitive to 50 mcg. of neomycin which is the reverse of the sensitivity results prior to therapy.

The staphylococci found in the single control specimen were sensitive to 5 mcg. of thiostrepton but resistant to neomycin. When staphylococci were found after therapy, they were resistant to thiostrepton in 3 patiens and sensitive to 50 mcg. in the fourth. Two of these same strains were resistant to neomycin and 2 were sensitive to 5 mcg. of neomycin.

All coliform organisms found in the control specimens were resistant to thiostrepton but all were sensitive at the 5 mcg. level to neomycin. This situation was essentially unchanged with regard to the coliform organisms found after therapy.

The 2 patients with clostridia in the control specimens had organisms sensitive to 5 mcg. of thiostrepton but resistant to neomycin. A similar sensitivity was observed in the one patient from whom clostridia were recovered after therapy.

Bacteroides from the control specimens of 4 patients were resistant to both drugs and in the other 3 patients were sensitive at different levels to both drugs. Bacteroides which appeared on the second day after therapy in one patient were sensitive to 50 mcg. of thiostrepton even though they had been resistant prior to therapy.

DISCUSSION

From this study of a small series of patients it would appear that the combination of thiostrepton and neomycin has provided control of the bacterial flora in the feces, that most of the organisms found in control specimens are likely to be sensitive to reasonable concentrations of one or the other of the drugs, and that resistance is not likely to develop during the short period of therapy required for intestinal antisepsis.

The absence of disturbing side reactions with this combination should be confirmed in a larger series of patients.

The poor absorption of thiostrepton from the gastrointestinal tract and the demonstrated in vivo activity against micrococci add to the desirable characteristics of this drug for preoperative intestinal antisepsis. The lack of absorption following oral administration would also tend to keep it from being used indiscriminately for a variety of infectious diseases. Thus thiostrepton would be less likely to set up a resistant bacterial population in those patients who might need such a drug than are the more commonly used broad spectrum antibiotics whose indiscriminate use has created the dangers of enterocolitis and other antibiotic-resistant infections of the gastrointestinal tract.

SUMMARY

1. Thiostrepton alone is an unsatisfactory agent for intestinal antisepsis.

2. Thiostrepton-neomycin is one of the effective combinations for preoperative preparation of the colon.

REFERENCES

1. Cohn, I., Jr., and Longacre, A. B.: Tetracycline (Achromycin)—Neomycin for Preoperative Colon Preparation, Arch. Surg. 72: 371, 1956.

2. Cohn, I., Jr., and Longacre, A. B.: Neomycin-Nystatin for Pre-Operative Preparation of the Colon, Am. Surgeon **22**: 301, 1956.
3. Cohn, I., Jr., and Longacre, A. B.: Preoperative Sterilization of the Colon. Comparison of Various Antibacterial Agents. Antibiotics Annual 1955-1956, New York, 1956, Medical Encyclopedia, Inc., p. 105.
4. Cohn, I., Jr., and Longacre, A. B.: Antibiotics in Colon Surgery, South. M. J. **49**: 1115, 1956.
5. Cohn, I., Jr., and Longacre, A. B.: Preoperative Sterilization of the Colon. Comparison of Various Antibacterial Agents. Antibiotics Annual 1956-1957, New York, 1957, Medical Encyclopedia, Inc., p. 253.
6. Cohn, I., Jr., and Longacre, A. B.: Chlorquinaldol (Sterosan) and Chlorquinaldol-Neomycin for Preoperative Preparation of the Colon, Gastroenterology **32**: 855, 1957.
7. Cohn, I., Jr., and Longacre, A. B.: Erythromycin and Erythromycin-Neomycin for Intestinal Antisepsis, Am. J. Surg. In press.
8. Cohn, I., Jr., and Longacre, A. B.: Novobiocin and Novobiocin-Neomycin for Intestinal Antisepsis, Ann. Surg. In press.
9. Pagano, J. F., Weinstein, M. J., Stout, H. A., and Donovick, R.: Thiostrepton, a New Antibiotic. I. In Vitro Studies, Antibiotics Annual 1955-1956, New York, 1956, Medical Encyclopedia, Inc., p. 554.
10. Steinberg, B. A., Jambor, W. P., and Suydam, L. O.: Thiostrepton, a New Antibiotic. III. In Vivo Studies, Antibiotics Annual 1955-1956, New York, 1956, Medical Encyclopedia, Inc., p. 562.
11. Vandeputte, J., and Dutcher, J. D.: Thiostrepton, a New Antibiotic. II. Isolation and Chemical Characterization, Antibiotics Annual 1955-1956, New York, 1956, Medical Encyclopedia, Inc., p. 560.

TUMEFACTIVE XANTHOGRANULOMATOUS PYELONEPHRITIS

DONALD W. SELZER, M.D.,* DAVID C. DAHLIN, M.D.,** AND
JAMES H. DEWEERD, M.D.,*** ROCHESTER, MINN.

THE opportunity to see and examine a patient (Case 1) 9 years after surgical and pathologic confirmation of the presence of an inoperable hypernephroma for which no irradiation treatment had been administered aroused our interest. The microscopic sections of tissue removed at operation were reviewed and revealed that the lesion was a peculiar proliferative inflammatory reaction. This reaction was characterized by an abundance of fat-laden macrophages which replaced the renal architecture and were accompanied by an infiltrate of plasma cells and lymphocytes. The lipophages were easily mistaken for the clear cells of renal carcinoma. These observations led us to further study of the condition.

It has long been known that foam cell granulomas can occur in the kidney. As early as 1916, Schlagenhaufer[11] reported 5 cases of pyelonephritis in which the microscopic appearance suggested actinomycosis because of tubercles with centers of clumped staphylococci surrounded by foam cells, lymphocytes, plasma cells, and fibrous tissue. Each of these lesions was proved to be caused by staphylococci on culture. Schlagenhaufer, therefore, suggested the name "staphylomycosis" and compared it to botryomycosis seen in domestic animals. Putschar,[10] in 1934, noticed that collections of foam cells resembling those of a hypernephroma occur around abscesses in pyonephrosis. The name "pyelonephritis xanthomatosa" was proposed by Österlind,[9] in 1944, as he presented 3 cases with the microscopic features mentioned. Additional reports,[1-7, 12] make a total of 24 similar cases which we have encountered in the literature. In several of these reports the gross or microscopic picture has been compared to that seen in renal tuberculosis, actinomycosis, or carcinoma.

We are reporting 7 cases (Cases 1 to 7) of chronic suppurative pyelonephritis in each of which some degree of granulomatous reaction was present and the most striking feature of the reaction was an abundance of lipide-laden foam cells. It is our purpose to emphasize the similarity of this disease to hypernephroma from the standpoint of the gross and microscopic appearance (Figs. 1 and 2).

CASE REPORTS

CASE 1.—A 66-year-old white woman was admitted to the Mayo Clinic, July 12, 1946. She complained of a dull ache in the left side of the abdomen near the iliac crest, of urinary urgency, and nocturia. This illness began with the sudden onset of severe left

The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.
*Fellow in Surgery, Mayo Foundation.
**Section of Surgical Pathology.
***Section of Urology, Mayo Clinic and Mayo Foundation, Rochester, Minn.
Received for publication Feb. 18, 1957.

abdominal pain one month previous to admission. The pain persisted for about 24 hours and required opiates for relief. Three or four hours after the pain began, the patient experienced a chill followed by fever. She was hospitalized and found to have gross hematuria. Subsequent retrograde urograms showed a shadow in the area of the lower calyx of the left kidney, interpreted as being caused by a stone, and a tract leading from the lower calyx to the perirenal region. The attending physician suggested the possibility of a tuberculous process and recommended exploration. The patient had been seen at the clinic in 1931 at which time a small density was noted over the lower pole of the left kidney on a plain roentgenogram of the abdomen. The remainder of the history and the family history were noncontributory.

Physical examination at the clinic gave essentially negative results except for moderate tenderness to percussion over the left costovertebral angle.

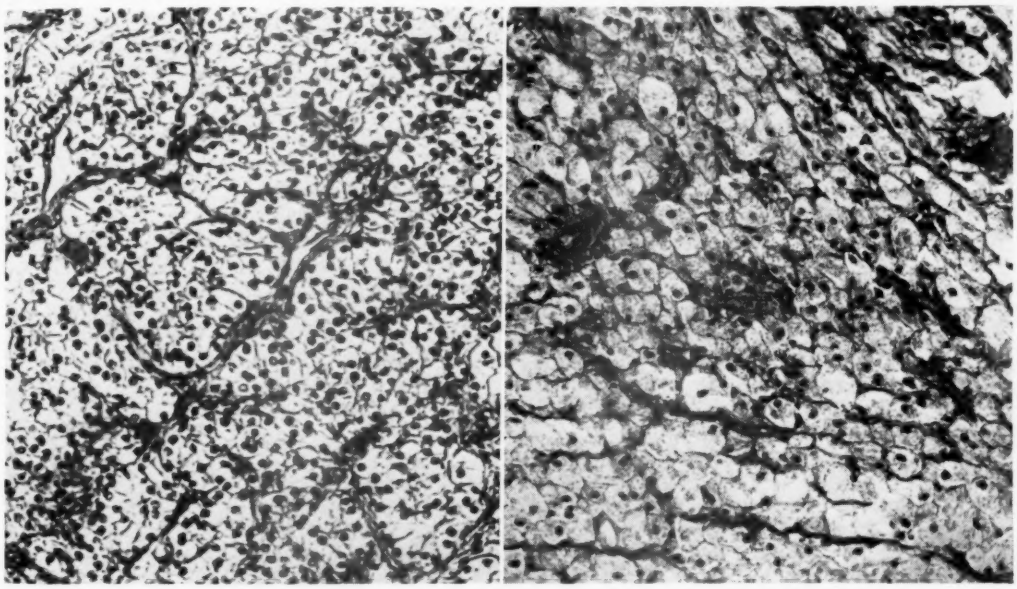


Fig. 1. Fig. 2.

Fig. 1.—Typical hypernephroma with large clear cells (hematoxylin and eosin; ×200).
Fig. 2.—Inflammatory lesion in Case 6. Similarity to Fig. 1 should be noted (hematoxylin and eosin; ×200).

Laboratory studies revealed albuminuria, grade 1 (on the basis of grades 1 to 4 of which grade 1 is the least and grade 4 the greatest), 20 to 50 leukocytes per high-power field and occasional erythrocytes in the urine. A culture of the urine was positive for *Escherichia coli* and *Pseudomonas aeruginosa*. The value for hemoglobin was 9.7 Gm. per 100 c.c. of blood, the erythrocyte count 2,880,000, and the leukocyte count 5,600 per cubic millimeter of blood. The sedimentation rate of erythrocytes was 132 mm. in one hour (Westergren). A smear of the peripheral blood was not diagnostic. The concentration of blood urea, and the carbon dioxide combining power were normal. A plain roentgenogram of the abdomen showed two dense shadows, 5 mm. in diameter, in the left renal area. An excretory urogram indicated a normal right kidney and ureter and an expanding lesion in the lower pole of the left kidney. The upper and middle calyces were stretched around the mass and the tips were dilated. The lower calyx was abbreviated. The urologist considered that the lesion was most likely to be a renal tumor with calcification, although inflammation and tuberculosis could not be excluded.

This patient had varying amounts of abdominal pain and soreness associated with low-grade fever during her stay in the hospital before operation. The anemia was corrected by

transfusion. On July 23, 1946, surgical exploration was carried out and a large adherent tumor mass was found in the left renal region. A specimen was removed and the microscopic interpretation was hypernephroma. The surgeon judged the lesion to be inoperable and the wound was closed. The patient made an uneventful postoperative recovery and was dismissed without further treatment.

This patient was next seen May 5, 1955, when she returned for a routine examination. She had been in excellent health following her dismissal 9 years previously and had no complaints other than transient vague mild ache in the left lower part of the abdomen. She had no urinary symptoms. Complete physical and laboratory examinations gave essentially negative results except for an indeterminate condition in the left kidney disclosed by excretory urogram. The tissue removed in 1946 was re-examined and further sections were prepared and the diagnosis was revised to xanthogranulomatous pyelonephritis.

At this examination, the specimen was found to consist of a number of nondescript grayish fragments. Microscopically, sheets of large foamy lipide-laden macrophages in no particular arrangement dominated the picture (Fig. 3). These macrophages were surrounded and infiltrated by cells of an inflammatory nature, mainly lymphocytes and plasma cells. The nuclei of the macrophages were regular in size, shape, and staining reaction and no mitotic figures were found. Identifiable renal parenchyma or capsule was not present.

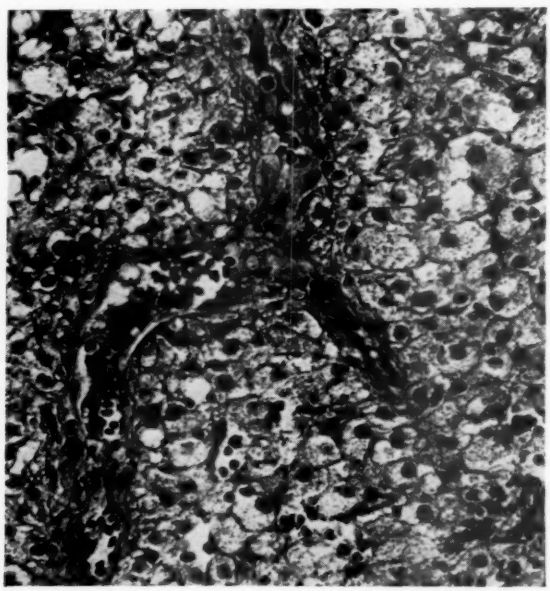


Fig. 3.—(Case 1.) Typical area which was originally mistaken for a hypernephroma (hematoxylin and eosin; ×275).

CASE 2.—A 48-year-old white man was admitted to the clinic April 4, 1950, because of pain in the left costovertebral angle, fever, and drainage from a wound in the left flank. This man's difficulty had been present for approximately 2 years previous to admission and had consisted of recurring episodes of pain in the left costovertebral angle, fever, and pyuria. The last such episode occurred in February, 1950, and after this episode a swelling developed in the left flank. He had been hospitalized and this area was drained surgically on March 4, 1950. He was well following this procedure until 10 days prior to admission when the symptoms recurred and drainage was noted at the site of the incision.

Significant physical findings on examination at the clinic were a draining sinus in the left loin and a fluctuant mass deep in the left side of the abdomen.

Urinalysis revealed specific gravity of 1.005, acid reaction, albuminuria, grade 1, and no sugar. Microscopically there were 1 to 8 erythrocytes per high-power field and the high-power field was three-fourths full of pus cells. The leukocyte count was 13,700. The concentration of hemoglobin and urea in the blood and the sedimentation rate of erythrocytes

Fig. 4.—(Case 2.) Tumefactive granuloma replacing a portion of the kidney. Cases 3 through 5 presented a similar picture.

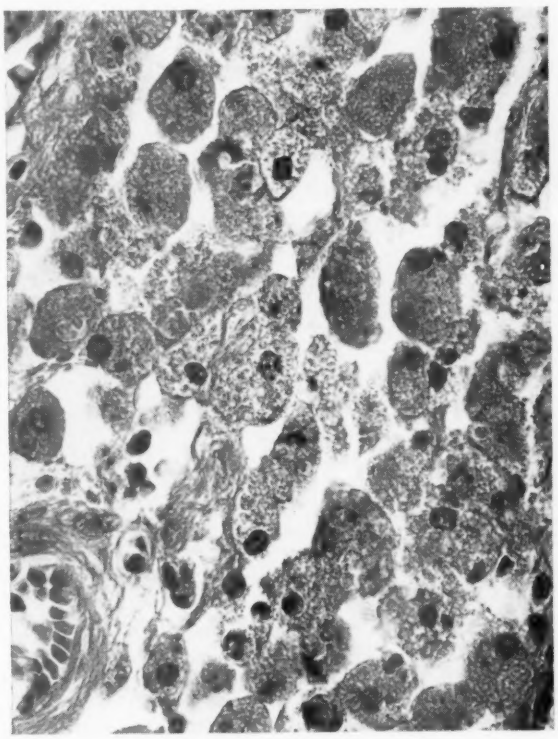


Fig. 5.—(Case 2.) Foamy granular cells dominated the histologic picture throughout (hematoxylin and eosin; ×475).

were normal. Excretory urograms indicated that the right kidney and ureter were normal. On the left the spreading and clubbing of the middle and lower calyces suggested an expanding intrarenal lesion.

A diagnosis of perirenal abscess was made, and the abscess was incised and drained on March 15, 1950. Biopsy at that time revealed inflammation and numerous foam cells. The patient was dismissed after an uneventful postoperative stay in the hospital.

On Aug. 21, 1950, the patient returned; he had remained well until August 4, when he experienced a chill followed by elevated temperature. One week later pain developed in the left flank, followed in a few days by drainage from the old wound. Physical, laboratory, and radiographic studies were essentially unchanged and a further trial of medical management was elected.

The patient returned on Nov. 12, 1950, because of persistent drainage from the old wound and mild pain in the left flank, slight fever, and night sweats. Left nephrectomy was performed November 15.

At re-examination in 1956 the specimen consisted of a firm, yellow, lobulated mass measuring 10 by 9 by 9 cm. which occupied the middle three-fifths of the left kidney and extended into the perirenal fat (Fig. 4). The capsular margin was indistinct because of involvement by the inflammatory process. Microscopic sections of the mass showed sheets of foamy cells containing pink granular cytoplasm with considerable numbers of finely divided fat droplets in the cytoplasm (Fig. 5). There was an accompanying infiltrate of lymphocytes and plasma cells. Stains for fat were strongly positive. There was little variation in the nuclei of the foam cells. Culture of pus taken at operation was positive for *Escherichia coli.*

CASE 3.—A 30-year-old white man registered at the clinic on Nov. 7, 1938, complaining of a heavy dull ache in the left flank associated with chills, sweats, and daily fever to 103° F. This illness began 8 weeks prior to admission with a sharp pain in the left flank which lasted 3 days. The patient had been hospitalized elsewhere and complete studies including excretory urograms and roentgenographic studies of the colon and stomach gave negative results. The only abnormal finding at that time was leukocytosis with the number of leukocytes varying from 18,000 to 22,000 cells per cubic millimeter.

The only positive physical finding was moderate tenderness to percussion over the left costovertebral angle.

Significant laboratory findings were a few pus cells per high-power field in the urine and a sedimentation rate of erythrocytes of 111 mm. in one hour (Westergren). Blood cultures evidenced no growth.

Excretory urograms showed a normal renal pelvis, calyces, and ureter on the right. On the left there was indefinite enlargement of the kidney with incomplete visualization of the upper and middle calyces and flattening of the lateral border of the renal pelvis.

Left nephrectomy was done Nov. 10, 1938, for tumor of the kidney of either inflammatory or neoplastic origin.

On re-examination in 1956, the left kidney contained a soft, yellow tumor 7 cm. in diameter in its upper portion. There was mottling with similar yellowish tissue throughout the remaining pyramids. The main mass extended peripherally beyond the confines of the kidney. The capsule was indistinct and the perirenal fat was firm for a distance of about 2 cm. beyond the margin of the kidney. Microscopic sections taken through the mass disclosed areas of confluent foamy lipophages accompanied by an infiltrate of plasma cells and lymphocytes. In areas there were focal collections of polymorphonuclear cells nearly to the point of forming abscesses. The perirenal fat contained an abundance of the same lipophages and inflammatory cells. Stains for fat of the sections taken through the mass were strongly positive. Cultures of the kidney taken at operation were positive for *Micrococcus pyogenes* var. *aureus (Staphylococcus aureus).*

CASE 4.—A 58-year-old white woman was admitted to the clinic Jan. 1, 1936. She complained of dull left abdominal pain of one month's duration which was relieved by

expelling flatus or a stool. In addition she mentioned anorexia and a loss of 10 pounds in a month. She had no urinary symptoms. Her home physician had referred the patient to the clinic for care because of an abdominal mass. She had had hypertension for 2 years with a systolic blood pressure as high as 220 mm. Hg. Two months prior to admission she had had a carbuncle on her left arm.

On physical examination the blood pressure was 160/90, with auricular fibrillation, and extension of cardiac dullness to the anterior axillary line. A firm mass approximately 10 cm. in diameter was present in the left subcostal region.

Urinalysis showed a specific gravity of 1.025, acid reaction, no sugar, albuminuria, grade 1, and no cellular elements. A routine stereoroentgenogram of the thorax revealed an enlarged heart. Excretory urogram indicated a tumor of the lower pole of the left kidney.

Left nephrectomy was done on Jan. 20, 1936, for a large mass in the lower pole of the left kidney which was adherent to the peritoneum and adjacent structures.

On recent restudy, sectioning of the removed left kidney disclosed replacement of a portion by a yellow mass 6 by 5 by 4 cm. The capsular margin of the kidney was indistinct and the perirenal fat was densely adherent over the region of the mass. Microscopic sections taken from the mass showed areas of foamy lipophages surrounded by and infiltrated by numerous lymphocytes and plasma cells. There were patchy areas of fibrous connective tissue. Sections taken at the outer margins of this mass showed a continuation of this process into the perirenal fat and the renal capsule was not recognizable.

CASE 5.—A 50-year-old white man was admitted to the clinic Dec. 20, 1918, complaining of pain and ache in the left flank. This illness had begun 2 weeks previously with sudden onset of severe colicky pain in the left flank without extension and was not associated with other symptoms. This pain persisted for about one week and was followed by a dull ache in the same region.

The only positive physical finding was the presence of a firm rounded mass in the left subcostal region that did not move with respiration.

Urinalysis revealed a specific gravity of 1.024, an acid reaction, no glycosuria, albuminuria grade 2, and 3 to 20 leukocytes per high-power field. The leukocyte count was 11,800 per cubic millimeter and 83 per cent were polymorphonuclear leukocytes. Retrograde urography indicated a normal right kidney. The left kidney was displaced laterally, the upper calyx was abbreviated, and the lower calyx was elongated; these observations were suggestive of the presence of a tumor of the left kidney.

At surgical exploration on Dec. 27, 1918, a large adherent inflammatory mass was exposed in the left renal fossa. Several blocks of tissue were removed for biopsy.

Grossly, there were several blocks of grayish-yellow firm tissue, about 7 cm. in diameter in aggregate. Microscopic examination of multiple sections disclosed a picture like that seen in the yellow mass in the preceding case.

CASE 6.—A 50-year-old white woman was admitted to the clinic Aug. 20, 1923, because of abdominal pain, weakness, and loss of weight. She dated the illness to March, 1922, at which time she experienced sudden severe pain to the left of the midabdomen. The pain lasted about 4 hours and was followed by soreness and tenderness in the same region which diminished over the next several days. Weakness and fatigue ensued. About 2 weeks prior to admission she again had an episode of severe left abdominal pain which extended into the left side of the back. Neither of these attacks was associated with chills or fever or any urinary symptoms. She had lost 40 pounds in the preceding year.

Physical examination revealed a chronically ill patient with evidence of loss of weight. A mass measuring about 12 cm. in diameter was palpated in the left subcostal region.

Notable features of the urinalysis were albuminuria, grade 1, occasional granular casts, and more than 50 leukocytes per high-power field. The concentration of hemoglobin was 44 per cent (Dare), the erythrocyte count was 3,770,000, and the leukocyte count was 10,600 per cubic millimeter of blood. Excretory urography indicated a functionless left kidney with multiple stones.

Fig. 6.—(Case 7.) Obvious inflammatory granulomatous lesions in the pyramids of a pyelonephritic kidney.

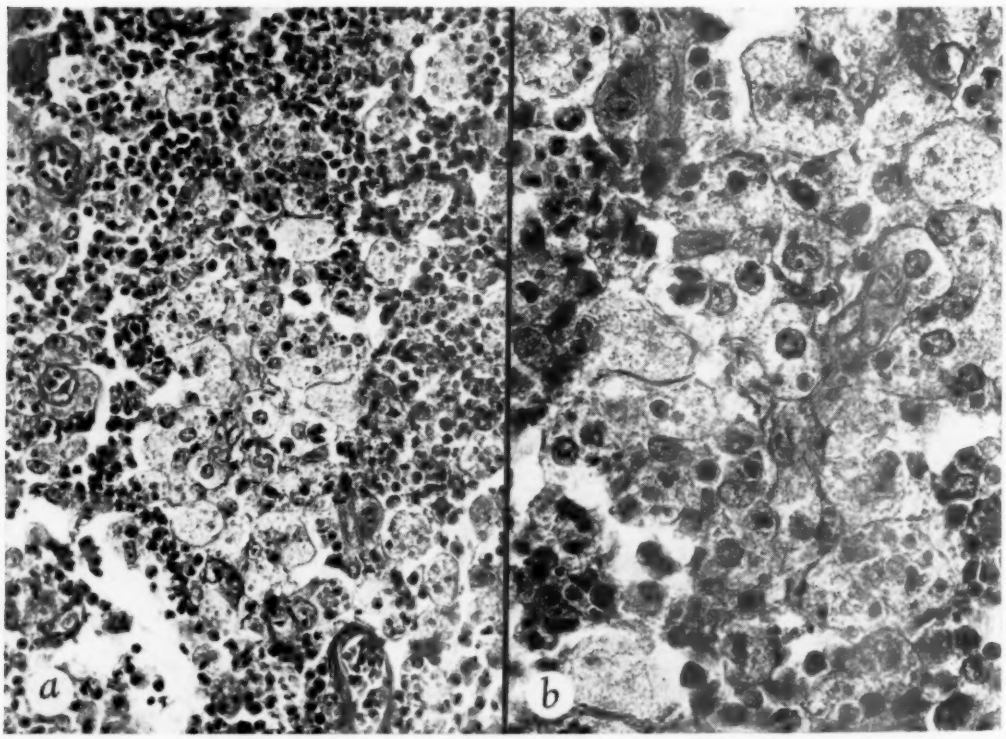


Fig. 7.—(Case 7.) *A*, A small nest of foamy cells may be seen in the center of the mass of plasma cells and lymphocytes (hematoxylin and eosin; ×250). *B*, The nest of cells seen in *A* (hematoxylin and eosin; ×475).

Left nephrectomy was performed on Aug. 28, 1923. On recent gross examination the removed kidney appeared somewhat enlarged and the pelvis was moderately dilated. On cross section, there were several stones in the pelvis. The entire substance of the kidney appeared to be replaced by granular yellow tissue. This tissue extended beyond the confines of the kidney and the capsule could not be identified. Microscopically there were confluent areas of chronic pyelonephritis with numerous sheets of lipophages resembling the cells in a hypernephroma (Fig. 2). The inflammatory process was characterized by plasma cells and lymphocytes. There were small scattered areas of calcification.

CASE 7.—A 70-year-old white man came to the clinic May 27, 1950, because of pain and aching in the left flank. From 1940 to 1949, he had repeated episodes of typical ureteral colic. In April, 1949, a left ureteral stone was removed surgically. This procedure was followed by purulent drainage from the wound for about 8 months. In April, 1950, moderate pain in the left abdomen developed gradually and a functionless left kidney was found.

Physical examination at the clinic disclosed normal conditions. Significant laboratory findings were albuminuria, grade 1, and 3 to 20 leukocytes per high-power field in the urine. The sedimentation rate of erythrocytes was 36 mm. in one hour (Westergren). The excretory urogram failed to show the left kidney. Left nephrectomy was performed May 27, 1950.

When the tissue removed was restudied in 1956, the kidney then weighed 100 Gm. On cut section the pelvis was dilated and the pyramids were nearly completely replaced by a granular grayish-yellow tissue (Fig. 6). Microscopic sections through the pyramids showed an abundance of inflammatory reaction, both acute and chronic. Nested in this inflammatory process were small foci of lipophages (Fig. 7, *A* and *B*). This whole reaction was superimposed on phantom architecture of the kidney. Stains for fat revealed a surprising amount of fat in this pyelonephritic process. Cultures made at operation were positive for *Aerobacter aerogenes*.

COMMENT

The first 6 of these patients had renal granulomatous lesions grossly indistinguishable from neoplasms. A granuloma is an inflammatory tumor. The seventh case is included as a rather ordinary case of subacute pyelonephritis which, however, shows a minimal degree of the granulomatous process and we consider that it represents a transitional stage and indicates the origin of the foam cells in areas of chronic inflammation. Barrie[1] described renal lesions similar to tuberculosis with tubercle formation. The epithelioid cells in his case resembled the foamy cells we have described. Mack and Mador[6] also noted that chronic suppurative pyelonephritis could simulate tuberculosis. In Schlagenhaufer's[11] cases there were tubercles with deep staining clusters in the centers which resembled the actinomycotic process. He proved that these central masses were colonies of staphylococci. Our cases were not characterized by formation of tubercles. Neither did we find giant cells or necrosis. The macrophages (epithelioid cells), heavy-laden with lipide, and the heavy infiltrate of round cells comprise the inflammatory tumor.

The etiology of this process remains obscure. Barrie[1] advanced the idea that the kidney is like the brain in that any degenerating disorder may show accumulation of lipide. Certainly there is merit in what he says since renal carcinoma and renal adenoma have cells with high fat content as does the pyelonephritis under consideration in this presentation. Schlagenhaufer's[11] 5 cases were all due to infection by staphylococci. Surgical cultures were made

in 3 of our cases and a urine culture in a fourth. Of these, only one was positive for staphylococci. Serologic tests for syphilis were negative in all 7 of our cases. Österlind[9] found renal or ureteral lithiasis in each of his 3 cases. Stones were found in only one of our 7 cases; a stone had been removed previously in a second; and there was radiographic evidence of stone in a third. The common denominator in our cases seems to be suppuration, usually of a prolonged nature. We advance this as the prime etiologic factor. Since reviewing the cases presented herein, we have been impressed with the frequency with which we find foam cells nested in involved areas of subacute and chronic pyelonephritis. Our hypothesis concerning suppuration as an etiologic factor augments rather than displaces those mentioned, as suppuration is commonly associated with renal lithiasis, and certainly staphylococci are not uncommon offenders in pyogenic affections of the kidneys. Aside from stones in 3 of our cases, the underlying cause of pyelonephritis was not apparent.

The origin of the foam cells provokes some interest. As has been mentioned we considered them to be macrophages, the "resting-wandering cells." Barrie[1] on the other hand was convinced that they were fibroblasts. He drew this conclusion because he failed to find blood monocytes in the infiltrate and because he demonstrated fat droplets in cells resembling fibroblasts. Indulgence in argument over origin of these cells is pointless since it is well accepted that both fibroblasts and tissue macrophages spring from a primitive mesenchymal tissue which has multipotentiality.[8]

Farrow and associates[4] attempted to show transition between this granulomatous pyelonephritis and renal lipomatosis or fatty replacement of the kidney. Of their 8 cases, 5 were fairly clear-cut examples of the disease discussed herein and 3 were plainly cases of fatty replacement of the kidney from the pelvic side, so-called renal lipomatosis. The transition is not clearly demonstrated. We found no evidence to support this contention in our cases. In a case or 2 the peripelvic fat seemed altered on gross examination, but without fail the picture was normal on microscopic examination. Since renal lipomatosis begins in the peripelvic fat, it is reasonable to expect some evidence of granulomatous change if a granulomatous process is etiologically responsible. We think that renal lipomatosis may follow any disease which causes atrophy of the kidney. Thus it might be the end point of this granulomatous process, not because of the lipophages and high fat content, but because of the resultant atrophy.

The similarity of xanthogranulomatous pyelonephritis to hypernephroma remains the impressive point. The clinical picture is consistent with that of hypernephroma as patients with that disease may have local pain and tenderness and elevation of temperature although chills and fever are unusual. Urographically a space-occupying lesion, whether an inflammatory or neoplastic tumor, usually distorts the renal architecture. From the standpoint of gross pathology a large, yellow, tumefactive mass replaces a portion of the kidney and may extend into perinephric tissues. Microscopically one is struck with a number of clear foamy cells arranged in sheets and cords associated with large

numbers of lymphocytes and plasma cells of the inflammatory reaction; at first glance the picture is similar to the picture of hypernephroma. However, close study fails to reveal any papillary or acinar arrangement of the cells. Furthermore, the nuclei are uniform in size, shape, and stainability and resemble nuclei of histiocytes.

The cases presented in this study were found with comparative ease by looking over a list of unclassified renal diseases. As mentioned, the condition in one of the cases had been erroneously diagnosed and indexed hypernephroma. It is likely that other cases are hidden under this diagnosis. It is also almost certain that a number of the cases reported in the literature of long-term survival in the presence of inoperable hypernephroma are in truth the result of mistaken diagnoses similar to ours.

SUMMARY

Seven cases of a condition that we choose to call tumefactive xanthogranulomatous pyelonephritis are reported together with a brief review of the pertinent literature. Renal suppuration is proposed as a prominent factor in pathogenesis. Grossly the lesion is a yellow tumor replacing a portion of the kidney. Microscopically the picture is that of a granulomatous reaction characterized by masses of lipide-containing macrophages with an associated inflammatory infiltrate. These foam cells are most likely "resting-wandering cells" and not true fibroblasts. No evidence was encountered in this study to support the contention that this condition is an early stage of renal lipomatosis. Emphasis has been laid on the close resemblance to hypernephroma.

REFERENCES

1. Barrie, H. J.: Foam-Cell Granuloma in Chronic Pyonephrosis Simulating Tuberculosis, Brit. J. Surg. **36**: 316-319, 1949.
2. Candiani, Angelo: Rara forma di granuloma renale aspecifico simulante un tumore maligno, Acta chir. ital. **11**: 121-137, 1955.
3. Cangelosi, J. T.: Replacement Lipomatosis Resembling Renal Tumor, U. S. Armed Forces M. J. **4**: 743-746, 1953.
4. Farrow, F. C., Cross, J. B., Tannhauser, S., and Andrews, J. T.: Renal Lipomatosis, New York J. Med. **49**: 2924-2932, 1949.
5. Ghosh, Hemprova: Chronic Pyelonephritis With Xanthogranulomatous Change: Report of 3 Cases, Am. J. Clin. Path. **25**: 1043-1049, 1955.
6. Mack, F. G., and Mador, M. L.: Pyogenic (Foam Cell) Granuloma in a Case of Pyonephrosis, J. Urol. **67**: 258-261, 1952.
7. Mathis, R. I., and Lorenzo, Jose: Absceso cortical de riñon simulando un neoplasma, Rev. argent. urol. **14**: 183-189, 1945.
8. Maximow, A. A., and Bloom, William: A Textbook of Histology, Philadelphia, 1952, W. B. Saunders Company, 592 pp.
9. österlind, Sture: Über pyelonephritis xanthomatosa, Acta chir. scandinav. **90**: 369-376, 1944.
10. Putschar, Walter: Die entzündlichen Erkrankungen der ableitenden Harnwege und der Nierenhüllen einschliesslich der Pyelonephritis und der Pyonephroses. In Lubarsh, O., and Henke, F.: Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin, 1934, Julius Springer, vol. 6, pt. 2, pp. 333-564.
11. Schlagenhaufer, Friedrich: Über eigentümliche Staphylomykosen der Nieren und des pararenalen Bindegewebes, Frankfurt. Ztschr. Path. **19**: 139-148, 1916.
12. Stout, A. P.: Tumor Seminar of Texas Society of Pathologists, Texas J. Med. **47**: 568-569, 1951.

TECHNIQUE FOR THE CORRECTION OF PECTUS EXCAVATUM

IVAN D. BARONOFSKY, M.D.,* SAN DIEGO, CALIF.

(From the U. S. Naval Hospital)

THE surgical correction of pectus excavatum has been established as an accepted procedure since 1939 when Oehsner and DeBakey,[3] and Lincoln Brown[1] published their reviews and series of cases. A variety of procedures have been proposed, notably those of Sweet,[5] Lester,[2] and Ravitch.[4]

We should like to present a technique for the correction of pectus excavatum, which, of course, has been borrowed from many of the techniques that have been suggested, but which in addition has certain modifications which we have found to be more anatomic and lend themselves to ease of performance. It is not our intention to discuss or argue the merits of indications for surgery in this condition. Suffice it to say that most of our patients have come to the surgeon either asking for relief of this condition or were brought by parents who desired its correction for them. Though patients with mild deformities were discouraged from having surgery, it was not easy to do this. It would appear that even after talking to patients or their parents and reassuring them, the deformity still is a tremendous psychologic hazard and its correction, even if it is minimal, is highly desirable. Another interesting aspect is the fact that in a large military installation the "grapevine" is highly developed, and one good technical result is enough to bring a number of patients to a surgeon. Other authors[4] have indicated that merit is to be derived from the surgical correction of pectus excavatum if it is done for (1) cosmetic, (2) orthopedic, and (3) physiologic reasons.

DESCRIPTION OF CASE MATERIAL

A total of 12 patients were operated upon. Half of these were adults. The youngest was 2½ years old and the oldest 42 years of age. All of the patients were in some way connected with the military, being dependents or retired or active duty personnel. Two of our patients had been operated upon previously, one twice.

OPERATIVE TECHNIQUE

Incision (See Fig. 1, *A* and *B*).—A transverse incision is made under intratracheal anesthesia. The lateral portions of this incision are placed in the inframammary fold. The length of the incision extends laterally, usually as far as the outer breast margins. Skin flaps are then developed superiorly and inferiorly in a plane superficial to the pectoralis major fascia. The superior limit of dissection is the second intercostal interspace. The inferior limit is

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

Received for publication April 1, 1957.

*At present, Chief, Department of Surgery, The Mount Sinai Hopsital, New York.

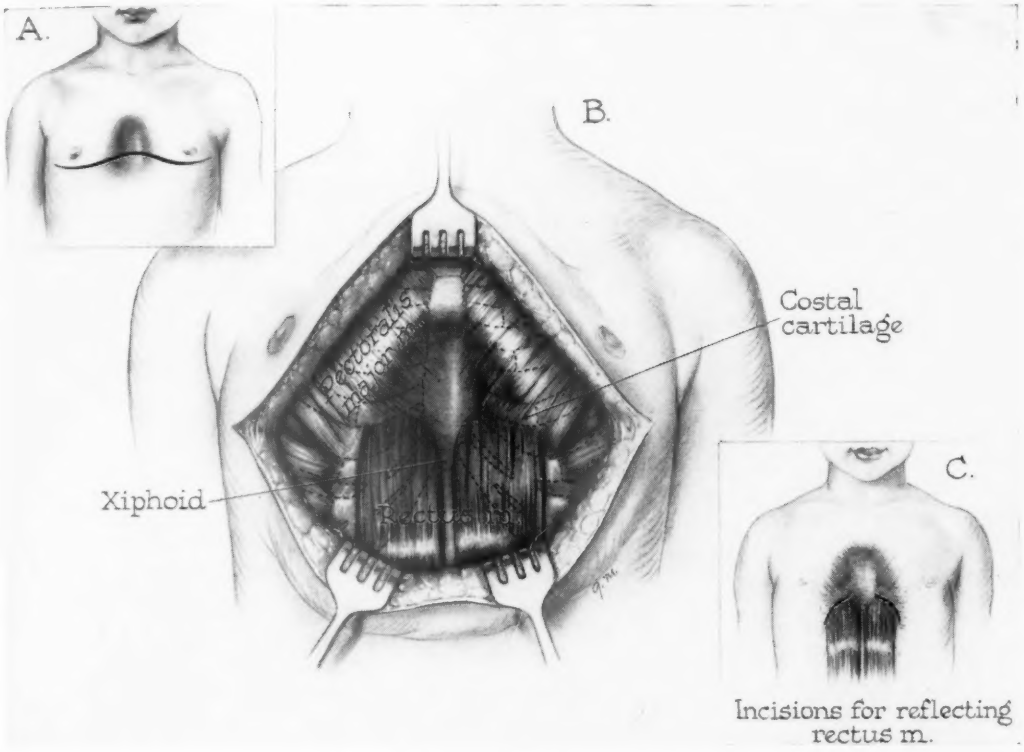


Fig. 1.—For explanation see text.

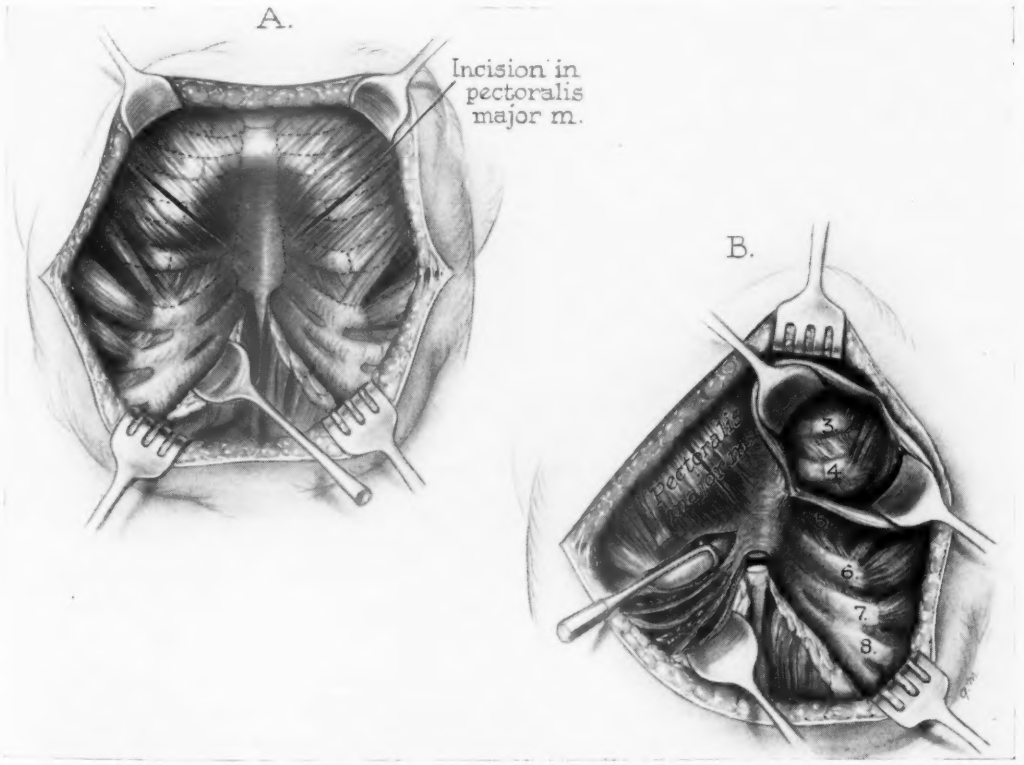


Fig. 2.—For explanation see text.

about 2 inches below the margin of the costal flare. The skin edges are carefully protected with moist saline packs. This incision is particularly advantageous in the female patient as only seminudity would disclose the incision.

Reflection of Rectus Abdominis Muscles (See Figs. 1, *C*, 2, *A*, and 4).—Anatomically the rectus muscles originate from as high as the fourth or fifth costal cartilage anteriorly. This fact is generally not mentioned in most descriptions. In order to resect the lower costal cartilages, the rectus must be reflected. A concave incision is made in such a manner that the rectus muscle is reflected medially toward the linea alba and xiphoid process. This maneuver uncovers the costal cartilages 4 or 5 to 8.

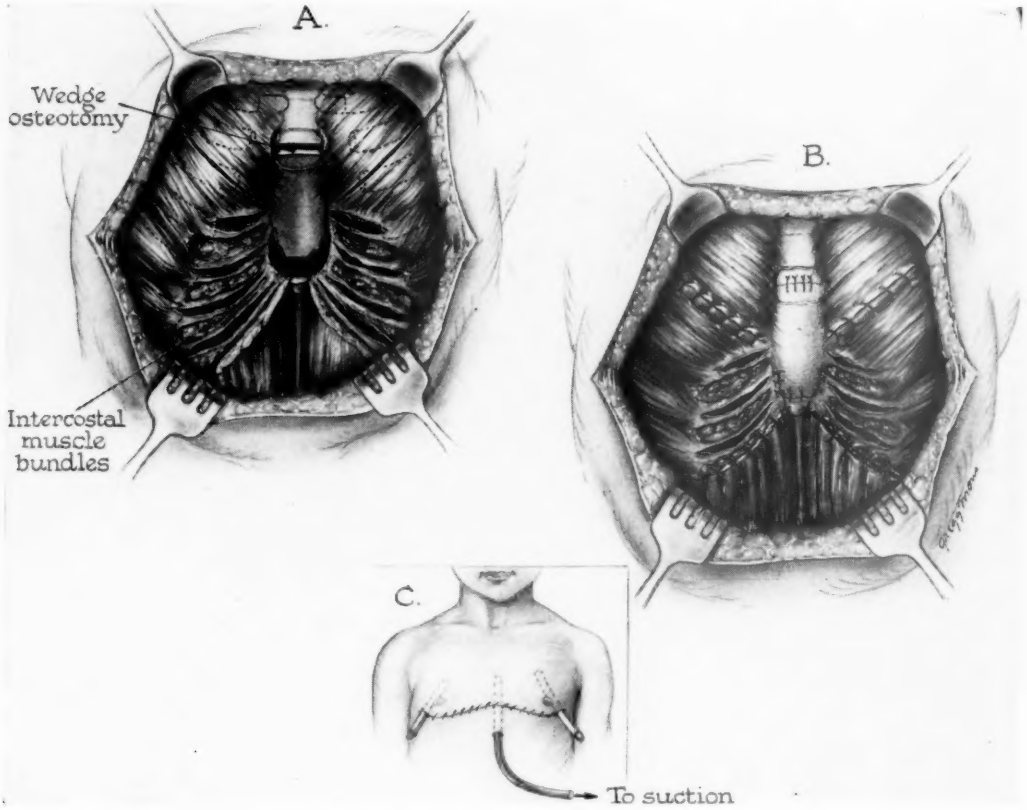


Fig. 3.—For explanation see text.

Resection of Costal Cartilages (See Figs. 2, *B*, and 3, *A*).—Once the lower costal cartilages are uncovered, the anatomic deformity is clearly demonstrated, a sharp declivity of the cartilages. The involved cartilages are removed in their entirety. It is to be emphasized that these should be removed in such a fashion that the perichondrium is left in place. It has been stated that in infants and children it is rather difficult to perform subperichondrial resection. It is our policy to save the perichondrium at all times. The number of cartilages resected will depend on how many are involved in the deformity. No set number should be removed. It is better to remove more than less. It is also wise to remove the entire costal cartilage and even some rib if necessary. Occasionally,

especially in older children and young adults, the declivity starts as far out as the midclavicular line and a much less than perfect result is obtained if resection of cartilage and rib are not extended to that area.

Incision of Pectoralis Major (See Fig. 2, *A* and *B*).—We have deviated from previous techniques at this point also. The pectoralis major muscle is not reflected from its origin on the sternum. Instead an incision is made in the direction of the muscle fibers. The length of the incision will depend on the size of the individual. However, the incision should be long enough so that ease in performing the subsequent maneuvers is possible. The incision starts from the sternal border and extends down to the ribs. By retracting the muscle edges, it is now possible to remove the upper costal cartilages. Usually the fourth and third costal cartilages are removed.

Fig. 4.—A photograph of the rectus muscles retracted off the costal flares. The costal flares can be seen as the inverted V in the center of the photograph and the rectus muscles are the tissues just below, closing the inverted V to form a triangle.

Freeing of the Sternum.—A finger is inserted laterally, if possible, under the xiphoid process and it is transected at its junction with the body. Its attachment to the rectus muscles and linea alba is left intact. As soon as the xiphosternal junction is transected, a marked elevation of the sternum occurs. It is now possible to insert a finger in the retrosternal area and free any other ligaments or attachments. The finger in most cases can be inserted as far as the sternal notch. The undersurface of the sternum should also be cleared laterally, trying to avoid entering the pleura. If a rent is accidentally made in the pleura, it may be widened so that any effusion will drain easily into the pleural cavity which in turn can be drained. If the rent is small, an attempt to close it, with the lungs expanded, can be made. In any event, entering the pleural cavity is not a serious matter if one recognizes the fact.

Elevation of Depression (See Fig. 3, *A*).—After the sternum is freed, a wedge cuneiform osteotomy is performed transversely through the sternum at the upper level of the sternal declivity. This is accomplished by first incising transversely the combined pectoralis major fascia and periosteum. The incision is carried down to the anterior cortex of the sternum. The periosteum is elevated superiorly and inferiorly with the help of periosteal elevators, for a distance of one centimeter, respectively. The wedge osteotomy is then performed. It is convenient to have a cuneiform osteotome for this maneuver; however, if this is not available, a straight one will serve the purpose. The osteotomy should be wide enough so that when the edges of it are approximated a fair overcorrection of the deformity is obtained. The osteotomy is made so that the posterior cortex is not cut.

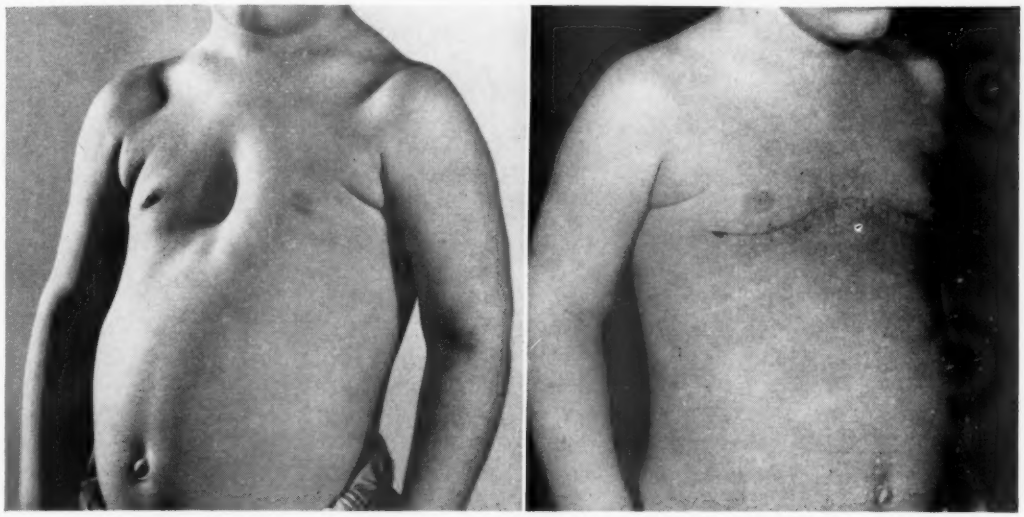
After the osteotomy is completed, the sternum is flexed anteriorly testing its final position. The lower 3 intercostal muscle bundles will in many instances tend to restrict the forced upward motion of the sternum. These are then sectioned right at the sternum. Suture ligature of the bundles is made as necessary. Three or four drill holes are placed above and below the osteotomy, protecting the heart underneath, and heavy (2-0) braided silk threaded through these with the help of a crochet needle. With the lower sternum held elevated by an assistant, the interrupted silks are tied so as to closely approximate the edges of the osteotomy. The periosteum is then closed with interrupted silk as is the fascia of the pectoralis major. The latter closures aid in holding the sternum in this corrected position.

Plastic Repair of Anterior Muscles (See Fig. 3, *B* and *C*).—Closure of the incision in the pectoralis major muscle is now accomplished with interrupted silk. The rectus abdominis muscles and the attached xiphoid process, if possible, are then sutured lightly to the edge of the sternum and to the adjoining intercostal muscle bundles. The latter are sutured to the edge of the sternum in such a manner that there is not too much tension on it. In general it can be stated that no attempt is made to follow a routine in this stage of the procedure, but rather to plasticize the anterior chest wall in such a manner that there will be no loose muscles left that may be a source of later poor cosmetic result. On occasion it may be necessary to leave the sternum displaced anteriorly without any muscles attached. A urethral catheter is threaded through a hole that may be available under the sternum and later will be brought out through a separate stab wound.

Skin and Subcutaneous Layer Closure (See Fig. 3, *C*).—After placing Penrose drains in the subcutaneous space and leading them out of the wound corners, the skin and subcutaneous layers are closed. On occasion the subcutaneous layer is tacked down to the fascia underlying in various places other than the wound edges, but in general only the wound edge is closed. A light dressing is applied.

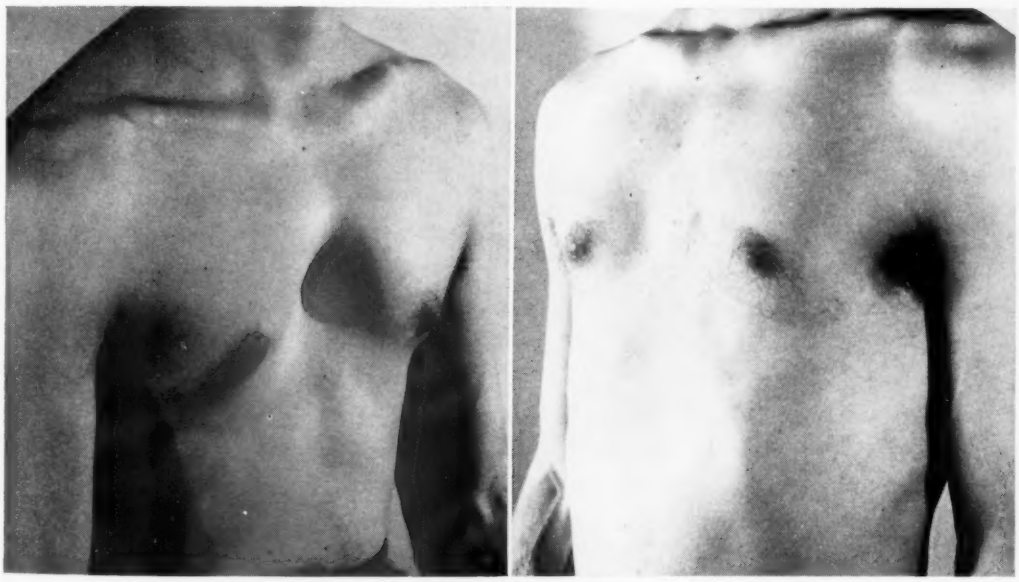
No external skin traction is used. However, on occasion in the children, we have placed a small protective loose cast over the upper chest as protection to the sternum. This is especially useful in the first few days following surgery

when the youngsters are up and around the wards and may trip and fall. On one occasion its presence in such an instance prevented any damage whatsoever. This cast, of course, is not used in the adult.



A. *B.*

Fig. 5.—M. P., aged 4. Views before (*A*) and one month after (*B*) surgery.



A. *B.*

Fig. 6.—W. K., aged 29. Views before (*A*) and 2 months after (*B*) surgery.

POSTOPERATIVE CARE

Antibiotics are given vigorously during the postoperative period. The suction tubes are removed when drainage has ceased (usually 2 to 3 days). Ambulation is encouraged as soon as the patient is awake. The soft rubber

drains are started out about the fifth day and are usually out by the eighth day. Physiotherapy is used on all cases with instructions to the therapist that the desire is to have the chest and abdominal muscles strengthened and the patients taught to keep their shoulders back and abdomens in.

POSTOPERATIVE COMPLICATIONS

There was no mortality in the 12 cases. Two complications were present following surgery. In one a subcutaneous wound infection cleared quickly with irrigations. The other was of more serious consequence and is to be considered a technical error. In the latter case, one of the first, the costal cartilages in an adult were resected with the perichondrium. The removal of the perichondrium resulted in a chest that was stable when no pressure was exerted on it; however, with pressure, the anterior chest wall could be easily depressed. A tantalum plate was inserted 8 months after the original surgery and good stability thus obtained. This complication has made us very careful in the removal of the cartilages. We insist on the perichondrium being left.

There were no cases of paradoxical motion of the chest wall following surgery. As a matter of fact there were no postoperative intrapleural complications.

RESULTS

The results were judged to be excellent in 10 cases, good in one, and poor in one. The poor one was the one mentioned previously with resection of the perichondrium. Cosmetically he had a perfect result; however, as mentioned previously, the anterior chest wall could easily be depressed. What we have classified as a good result is an adult who had been operated upon previously by another surgeon and the entire xiphoid removed. Because of a poor cosmetic result, he was reoperated upon and an excellent position of the sternum obtained; however, because of the absence of xiphoid, there was an unfilled depression immediately under the lower end of the sternum.

It is of interest to mention that in the one adult female operated upon (28 years of age) the prevalent off-the-shoulder dresses can be worn without any evidence of scar showing. It is also of interest to mention that the transverse scar under the breasts seems to have less keloid formation than the vertical midline scar.

SUMMARY

A technique for the correction of pectus excavatum is presented. This technique was used on 12 patients, and these included 6 adults and 6 children. The adult age range was from 19 to 42; the children ranged from 2½ to 5 years of age. Age was not considered a contraindication to surgery provided other findings were within normal limits. There was one serious technical error in the series of patients and this was related to the removal of the perichondrium. There was no operative mortality or serious morbidity in the series presented.

REFERENCES

1. Brown, A. Lincoln: Pectus Excavatum, J. Thoracic Surg. **9**: 164, 1939.
2. Lester, C. W.: The Surgical Treatment of Funnel Chest, Ann. Surg. **123**: 1003, 1946.
4. Ravitch, M. M.: The Operative Treatment of Pectus Excavatum, Ann. Surg. **129**: 429, 1949.
3. Ochsner, A., and DeBakey, M.: Chone-Chondrosternon, J. Thoracic Surg. **8**: 469, 1939.
5. Sweet, R. H.: Pectus Excavatum, Ann. Surg. **119**: 922, 1944.

EXPERIMENTAL STUDY OF THE FUSION OF THE MITRAL ANNULUS AT THE SITE OF POLAR CROSS PLICATION IN DOGS

RICHARD A. GILMAN, M.D.,* BENJAMIN G. MUSSER, M.D.,** JOSEPH E. IMBRIGLIA, M.D.,*** MANUAL J. VAZQUEZ, M.D.,**** AND HENRY T. NICHOLS, M.D.,***** PHILADELPHIA, PA.

POLAR cross fusion of the mitral annulus fibrosus has been used by Nichols[3] with encouraging clinical and physiologic results in mitral insufficiency. During the period of experimental and clinical evaluation, it was believed that the ultimate success of the procedure would depend upon the actual establishment of fusion of the approximated portions of the annulus by fibrous tissue growth. In order to study this factor, polar cross plication was carried out in dogs. Previously, Bernheim[1] had carried out experimentally a similar procedure in an attempt to create mitral stenosis in dogs. The possibility of actual fibrous union was not studied at that time. Kay[2] has performed a clinical operation which narrows the annulus but does not appear to bring the opposing sides of the annulus together to allow fusion.

METHOD OF STUDY

Twenty-four unselected mongrel dogs were subjected to posterior polar cross plication of the mitral annulus as devised by Nichols. In half of the animals, the annulus was plicated with Dacron suture alone, and in the rest with Dacron completely ensheathed within a strip of pericardium. Only the posterior one-fifth of the annulus was plicated so as to avoid the possibility of producing a physiologic degree of stenosis in the normal dog. The Dacron suture used is 80 pound test braided fishing line.† This size was chosen because of its large diameter as well as its strength. Smaller diameter sutures in the constantly moving heart might tend to cut through the annulus and to allow the divided ends to separate. Wrapping the suture with pericardium was based upon our belief that it would undergo fibrous infiltration, would tend to stimulate fibrosis,

This work was supported by the Mary Bailey Foundation for Heart and Great Vessel Research, the Institute for Cardiovascular Research of Hahnemann Medical College and Hospital of Philadelphia, and the Pennsylvania National Heart Institute Grant No. H2003C.

Received for publication, Feb. 8, 1957.

*Resident in Thoracic Surgery, Hahnemann Medical College and Hospital of Philadelphia; National Heart Institute Trainee.

**Resident (former) in Thoracic Surgery, Hahnemann Medical College and Hospital of Philadelphia. Now Chief of the Cardiovascular Services of the Harrisburg Hospital and the Harrisburg Polyclinic Hospital, Harrisburg, Pa. This work was done during the tenure of a National Heart Institute Traineeship.

***Acting Head, Division of Pathology, and Professor of Pathology, Hahnemann Medical College and Hospital of Philadelphia.

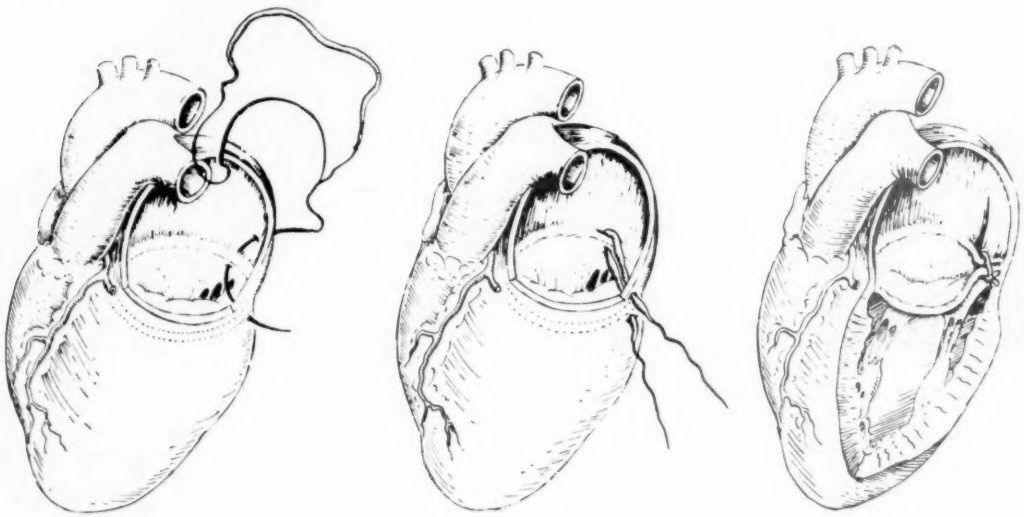
****Fellow in Thoracic Surgery, Bailey Thoracic Clinic.

*****Instructor, Department of Thoracic Surgery, Hahnemann Medical College and Hospital of Philadelphia, and Surgeon, Bailey Thoracic Clinic.

†Available from the Gudebrod Brothers Silk Company, Philadelphia, Pa.

and would act as a bridge for fibrous ingrowth in the event of subsequent separation of the annulus margins. Dacron was chosen in preference to nylon because it will not stretch.

The operation was essentially the same as that previously described by Nichols.[3] With a finger tip inserted into the left atrium through an incision made in the tip of the left auricular appendage, a suture was passed through the left atrial wall, was guided under two portions of the annulus, and finally emerged through the left ventricular wall close to the atrioventricular groove (Fig. 1, *A*). The end protruding from the atrial puncture was rethreaded and inserted through the original entrance hole. When the needle tip was felt within the chamber, it was directed by the finger to pass above the medial and mural portions of the annulus and then out through the ventricular wall as close to the other end of the suture as possible (Fig. 1, *B*). The suture was tied down tightly in increasing increments until it had cut through all intervening ventricular tissue and included the two portions of the annulus only (Fig. 1, *C*). The finger within the heart determined that the annulus had



A. *B.* *C.*

Fig. 1.—*A*, Dacron suture with a needle swedged on each end is used. The first needle is directed through the atrial wall and made to encircle the annulus posteriorly on the septal leaflet side. This needle then is directed across the atrial cavity to pass on the ventricular side of the mural portion of the annulus and then to emerge from the heart.

The second needle is engaged into the Dacron suture and then is made to enter the atrium through the original puncture site. This needle is made to emerge from the heart by passing it on the atrial side of the mural annulus.

The entire suture is passed into the atrium by engaging the second needle in the suture as shown, then pulling the pericardium-ensheathed Dacron suture through the atrial wall. *B*, The correct placement of the suture is demonstrated. *C*, Tying the suture produces close apposition of the annulus at the site of cross plication.

become approximated fully. Actual physical contact of the two apposed points upon the annulus is considered imperative to the success of this procedure. If the edges are not approximated, tissue growth cannot span the gap, at least not when plain suture material is used. The suture loop should not include any portion of the atrial wall. It must be tied tightly enough to cut through

any included ventricular wall tissue. If this is not accomplished initially, the remainder of the wall gradually cuts through, then the approximated portions of the annulus will separate before fibrous union can occur.

The dogs were sacrificed at intervals of 7 days to 3 months.

RESULTS

At 7 days there was the appearance of early granulation tissue and fibrous growth, but it was insufficiently strong to hold the annular tissue together without the presence of the suture. By the end of 3 weeks, a fibrous bridge had formed which was strong enough to hold the edges of the approximated annulus without the presence of the suture. After one month to 6 weeks, a dense scar was present which grossly was very hard and surrounded the entire portion of the annulus which had been occluded (Fig. 2).

There was no difference grossly between the amount and density of the fibrosis produced when the plication was produced with the suture material alone and that stimulated by suture wrapped with pericardium.

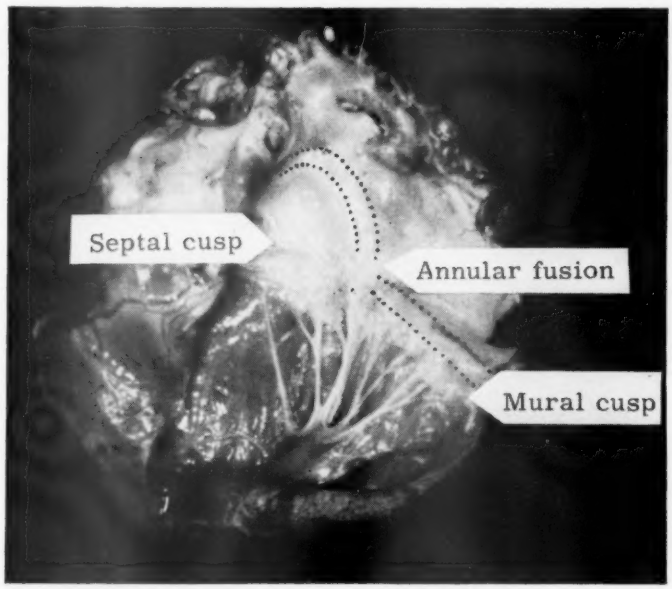


Fig. 2.—A smooth, dense cicatrix is demonstrated in the annulus at the arrow. Polar cross plication had been done 6 weeks previously.

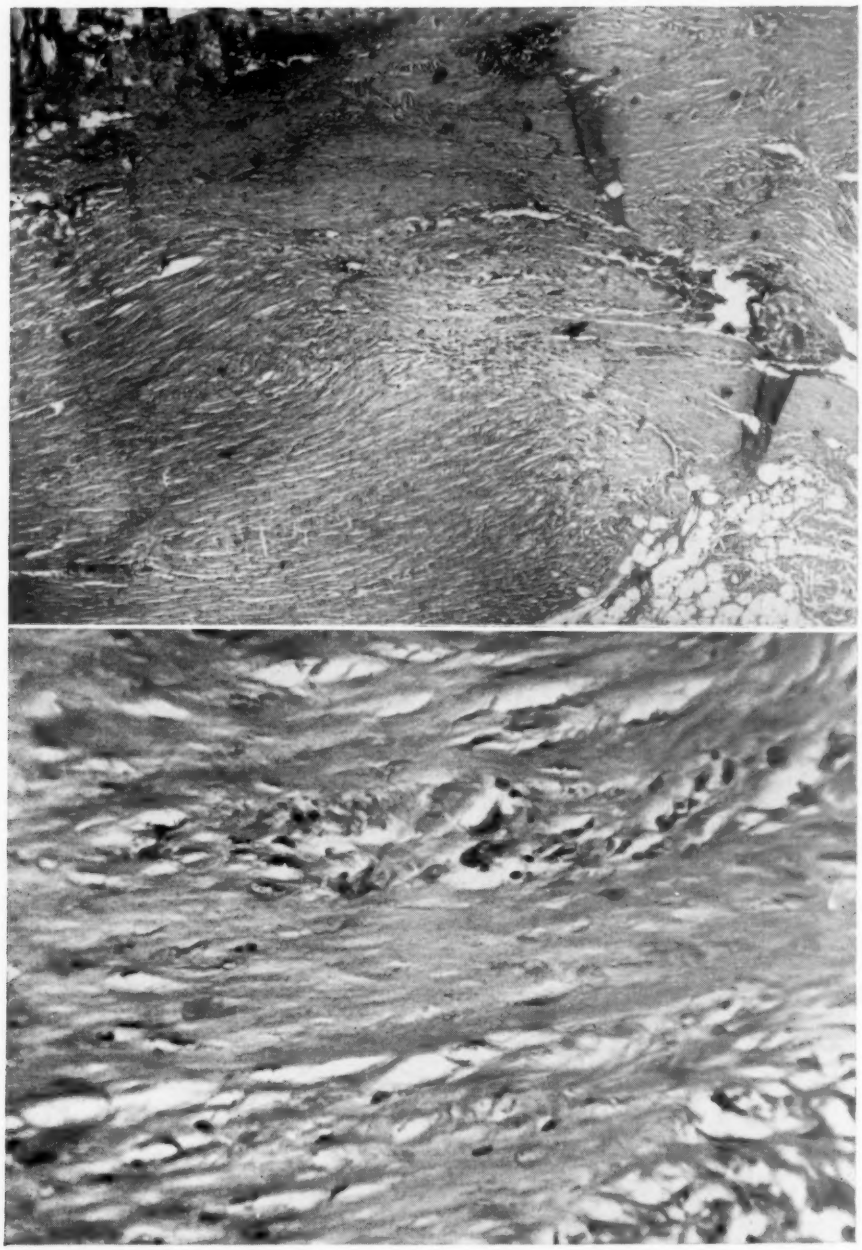
Sections were taken from the hearts at 3, 4, and 6 weeks, respectively. They showed proliferation of dense fibrous tissue (Fig. 3). There did not appear to be significant difference in the amount of fibrous tissue growth which was caused by the plain suture and that by suture wrapped in pericardium.

COMMENT

One of the logical points of question in the operative procedure of polar cross plication of the mitral annulus is whether the approximated surfaces of the annulus will become joined by a strong fibrous bridge. If the operative

procedure were to depend upon the holding power of the suture alone, in the constantly moving heart there is a strong probability that eventually it would cut through the annulus and permit re-establishment of the original degree

A.



B.

Fig. 3.—Microscopic sections through the cicatrix at the site of cross fusion are shown. These were taken from the specimen shown in Fig. 2. *A*, This shows the site of polar plication at a magnification of 28 diameters (reduced ¼ off). A cross section of the suture material is demonstrated. *B*, High-power examination shows dense cicatrix at the site of plication (×175, reduced ¼ off).

of incompetence, or perhaps even a greater one. In the experimental animal, sufficient growth of fibrous tissue occurs within 3 weeks to bind the annulus. By the end of one month, there is a dense fibrous scar. The presence or absence of pericardial encasement about the suture did not seem to alter the amount of fibrous union either in time of development or in the quantity produced. Whether this will apply in human subjects with the sometimes extremely dilated annulus of mitral regurgitation only can be conjectured at this time. Another theoretical advantage for the use of pericardium might exist clinically. If the suture should slip or if extra muscular tissue inadvertently were included within the suture loop so that the approximated surfaces of the annulus were to become separated subsequently, the pericardium might serve to function as a connecting bridge of living tissue for fibrous growth whereas the plain suture would not. Thus, although the use of pericardium does not, in the dog, increase either the amount of fibrous union or the speed of development, it may add a margin of safety in the human patient with clinical mitral regurgitation.

SUMMARY

1. Polar cross plication of the mitral annulus was performed in 24 dogs.
2. Plain Dacron suture and suture wrapped with pericardium were used.
3. Both appeared to stimulate fibrous union of the opposed annulus which was strong enough by 3 weeks to prevent separation of the surface.

REFERENCES

1. Bernheim, B. M.: Experimental Surgery of the Mitral Valve, Bull. Johns Hopkins Hosp. **20**: 107, 1909.
2. Kay, Earle B., and Cross, F. S.: Surgical Treatment of Mitral Insufficiency. SURGERY **37**: 697, 1955.
3. Nichols, H. T.: Mitral Insufficiency—Treatment by Polar Cross-Fusion of the Mitral Annulus Fibrosus, J. Thoracic Surg. **33**: 102, 1957.

A FILMER FOR THE STATIONARY SCREEN OXYGENATOR

ROBERT M. ANDERSON, M.D., DONALD P. ANDERSON, AND
JEROME HAROLD KAY, M.D., LOS ANGELES, CALIF.

(From the Department of Surgery of the University of Southern California School of Medicine)

IN 1951 Gibbon[1] described the stationary screen oxygenator. The modification of this apparatus reported in 1956 by Kay and Gaertner[2] has proved clinically to be very satisfactory. Recently we have developed a device which readily establishes a film of blood on the screens and thereby further simplifies the use of this apparatus. This device or filmer (Fig. 1) consists of a sheet of ¼-inch thick Lucite with $\frac{3}{32}$-inch wide slots. There are stainless steel rods at each end of the filmer. These allow the filmer to be raised to the top of the screens and lowered to the bottom of the screens. The filmer* is diagramed in place with the screens in the slots in Fig. 2.

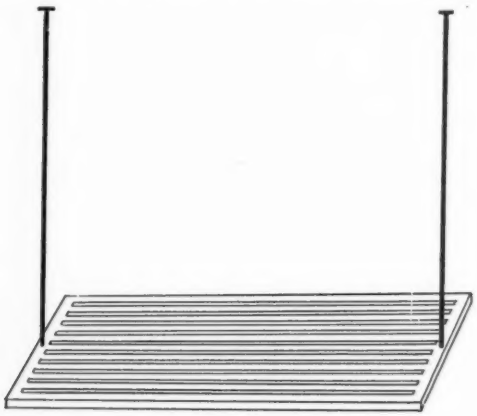


Fig. 1.

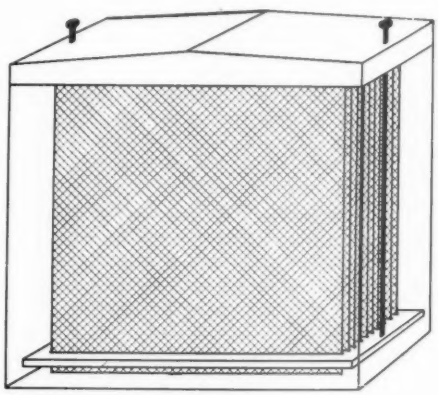


Fig. 2.

Fig. 1.—Lucite filmer with slots for the screens and stainless steel rods on either end for raising and lowering the filmer.

Fig. 2.—Filmer in place with the screens in the slots.

Just prior to starting extracorporeal circulation the filmer is raised to the top of the screens. The recirculating pump is started. A small pool of blood is maintained above the filmer by capillary attraction and as the filmer is lowered this establishes a film on the screens.

This technique has many advantages over the older method which consisted of filling the entire chamber containing the screens with saline. This

Aided by Grant No. 785 from the Attending Staff Association of the Los Angeles County Hospital.

Received for publication June 20, 1957.

*The filmer was kindly constructed for us by Corco of 2112 Midvale, Los Angeles 25, Calif.

chamber was emptied rapidly of its saline, thereby leaving a film of saline on the screens. As the saline was drained blood was pumped into the distribution chamber and a film of blood replaced the film of saline.

The new method employing the filmer has the following important advantages:

1. Saline is not used; therefore (a) no blood is discarded with the waste saline and (b) blood is not diluted with saline.

2. The filming process can be performed immediately prior to beginning extracorporeal circulation. This allows the pumps to be running for only that length of time that the patient is on extracorporeal circulation. This reduces to a minimum the duration of recirculation of blood in the pump-oxygenator.

3. It is time saving and simple and requires only a few seconds and replaces a cumbersome procedure.

4. Even though the film has never been broken in 50 procedures, the filmer is a safety factor as the film can be re-established within seconds at any time.

SUMMARY

A device which produces a film of blood on the stationary screen oxygenator by a simple method is described.

We express our gratitude to Mr. Larry Xavier for his technical assistance.

REFERENCES

1. Gibbon, J. H., Jr.: Application of a Mechanical Heart and Lung Apparatus to Cardiac Surgery, Minnesota Med. 37: 171, 1954.
2. Kay, J. H., and Gaertner, R. A.: A Simplified Pump-Oxygenator With Flow Equal to Normal Cardiac Output, Surgical Forum 7: 267, 1957.

INTERATRIAL VENOUS TRANSPOSITION

A One-Stage Intracardiac Operation for the Conversion of Complete Transposition of the Aorta and Pulmonary Artery to Corrected Transposition: Theory and Clinical Experience

K. Alvin Merendino, M.D., John E. Jesseph, M.D.,* Paul W. Herron, M.D.,* George I. Thomas, M.D.,* and Roy R. Vetto, M.D., Seattle, Wash.

(From the Department of Surgery, University of Washington School of Medicine)

IN PATIENTS with transposition of the great vessels, the left ventricular output through the pulmonary artery returns via the pulmonary veins to the left atrium, and blood leaving the right ventricle through the aorta returns to the right atrium via the superior and inferior venae cavae. Survival is impossible unless some type of communication exists between the left and right sides of the heart. In the usual type of transposition, these defects in their order of frequency are patent foramen ovale and/or interatrial septal defect, patent ductus arteriosus, and interventricular septal defect. In the collected review reported by Hanlon[6] a single lesion existed in 30 per cent of patients (10 per cent patent ductus arteriosus, 10 per cent interatrial septal defect, 10 per cent interventricular septal defect). The majority of patients with uncomplicated transposition exhibit a combination of any two or all three of these defects. In over-all occurrence, a patent foramen ovale or interatrial septal defect occurs in 75[6] to 100 per cent[11] of patients, a patent ductus arteriosus in 64[6] to 70 per cent,[11] and an interventricular septal defect in 44[6] to 55 per cent[11] of patients. Approximately 80 per cent of all patients with transposition exhibit one or more of these 3 defects. Some of these defects are considered minor and insufficient to interfere with a relatively normal life if the transposition were corrected. In the remaining 20 per cent, other major abnormalities exist.[10, 11] The latter group will not be discussed further, for they do not represent the usual type of transposition encountered.

Because complete transposition is not reproducible in the experimental laboratory, the attempts surgically to define a corrective operation, of necessity, have been made clinically. The clinical approach can be justified on other grounds as well. The average life expectancy of patients with transposition is 19 months. When those few patients surviving the first decade of life are excluded, the average survival is 5.5 months.[5] Lillehei and Varco[9] reporting new cases plus a collected series of Kato (also included in Hanlon's series) noted that only 4 per cent of their series were alive at 7 years of age and 78 per cent

Supported in part by U. S. Public Health Service Grant H-1110, funds from the Washington State Heart Association, and 171 funds from the State of Washington for Research in Biology and Medicine.

Received for publication June 29, 1957 .

*U. S. Public Health Service Postdoctorate Research Fellow of the National Heart Institute.

of the group had died during the first year of life. The fact that stillbirths are extremely rare, plus the fact that transposition now is recognized as a common congenital malformation of the heart, should be incentive enough to continue the clinical approach in search for a satisfactory procedure.

The previous surgical attempts to correct transposition fall into two main categories: (1) a rearrangement of the trunks or flow patterns of the aorta and pulmonary artery, and (2) the enlargement of existing defects or the creation of defects between the left and right heart with and without partial transposition of the systemic and pulmonary venous return.

In transposition, the systemic and pulmonary venous return is normal. Because the abnormality involves only the aorta and pulmonary artery, the correction of the difficulty appears simple. The obvious approach would be to transect these two main vessels with reanastomosis of the vessels in a switch-over fashion so that the distal aorta is sutured to the proximal pulmonary artery, and the distal pulmonary artery is anastomosed to the proximal aorta. A direct attempt to do this has been made by Bailey and associates,[2] utilizing hypothermia, and Mustard and co-workers,[11] using extracorporeal methods with a monkey lung. Others, namely Kay and Cross,[8] and Björk and Bouckaert,[3] experimentally by transection of the aorta and pulmonary artery using external grafts, have altered the flow patterns and accomplished hemodynamically the same physiologic state as a switch-over anastomosis. No survivals have resulted from these direct attempts to correct the arterial side of the circulation.

As experience has accumulated, it has become apparent that alterations involving the aorta and pulmonary artery cannot be successful. Of foremost importance is the fact that the coronary arteries arise from the aorta[2, 9, 11] and it is impossible to transfer the coronaries with the aorta. The mere switch-over of the major trunks would result in the coronaries receiving desaturated blood, a situation worse than the existing transposition. Second, the right ventricle by necessity has become the systemic chamber. The muscular hypertrophy is readily apparent and the force of contraction is evidenced by the ability of the right ventricle to maintain a systemic pressure. With a switch of major arterial channels, the work requirements of both right and left ventricles suddenly are changed. The left ventricle is unprepared to maintain a systemic pressure and the right ventricle now propels blood to the lungs with a systemic ejectile force. Hypotension and pulmonary edema would be expected to follow immediately. There are minor technical factors, such as the marked disparity in size of the 2 vessels commonly noted; these are of secondary importance, however.

The interest in creating new defects between the right and left sides of the heart with and without partial transposition of venous return was initiated by Blalock and Hanlon.[4, 6] Actually, attention to completion of the transposition by altering the venous return was made prior to the attempts to switch the major arteries. As it has become apparent that the latter does not appear feasible, efforts have been renewed to rearrange venous flow patterns. Since the earlier efforts, Lillehei, Varco, and co-workers,[9, 10] and, more recently, Baffes[1] have contributed to our knowledge and the problems involved in partial transpositions of the venous return. It is of interest that while the mortality has

been high, some survivors have been improved; however, there is no case in which complete venous transposition has been accomplished. Furthermore, as multiple operations are necessary with extracardiac maneuvers, one might expect that with each additional operation the mortality rate will be compounded and the eventual success rate small. Nonetheless, there appears to be agreement that the approach most likely to be successful is transposition of the venous return to correspond to the arterial transposition. The net effect is the conversion of complete transposition to corrected transposition. Corrected transposition is said to be compatible with a normal life expectancy.[5]

In all previous attempts to correct complete transposition of the major vessels, the procedures have been extracardiac. Because of the disadvantages of multiple-staged operations and the patent advantages of a one-stage procedure, our efforts have been directed to the intracardiac manipulation of flow patterns which result in complete transposition of the venous return to match the arterial transposition.

Our purpose is to describe a one-stage operation, namely, interatrial venous transposition for the conversion of complete transposition of the major arteries to corrected transposition using a pump-oxygenator, and to report preliminary clinical experience.

THE PROSTHESIS

In designing an interatrial prosthetic septum, it was necessary to satisfy several theoretical requirements. To function as intended, the prosthetic device must be smoothly curved in all its planes, presenting no surface irregularities which might serve to establish turbulence and consequent thrombus formation. It is also necessary to repartition the common atrial chamber (resulting from excision of the interatrial septum) so that approximately half the total volume of the chamber is allotted to each side. This is thought to be important in terms of diastolic atrial and ventricular filling pressures. Since intra-atrial pressures are low and almost equal bilaterally, a pliable, flexible prosthesis will not deform and will be more easily tailored to fit minor variations in inner contour of the atria.

By study of human and dog hearts, as well as making internal casts of the atria and great veins, a multi-curved septal form was devised to reverse bidirectionally the cardiac venous inflows. The material, the stages in the development of the final prosthesis, as well as the die used are depicted in Figs. 1, 2, 3, 4, and 5. The present die is made of dental casting compounds, intended for temporary use only. This die is being replaced by one of cast resin which will be more permanent and less fragile.

In final form, the prosthesis satisfies all the criteria outlined. Further, it has enough elasticity and latitude of dimension so that it can be trimmed and adjusted to fit atria of a wide range of internal dimension. The cupped "tail" of the prosthesis can be shortened to accommodate closely grouped pulmonary vein orifices and the edges of the caval arms can be cut away to fit almost any

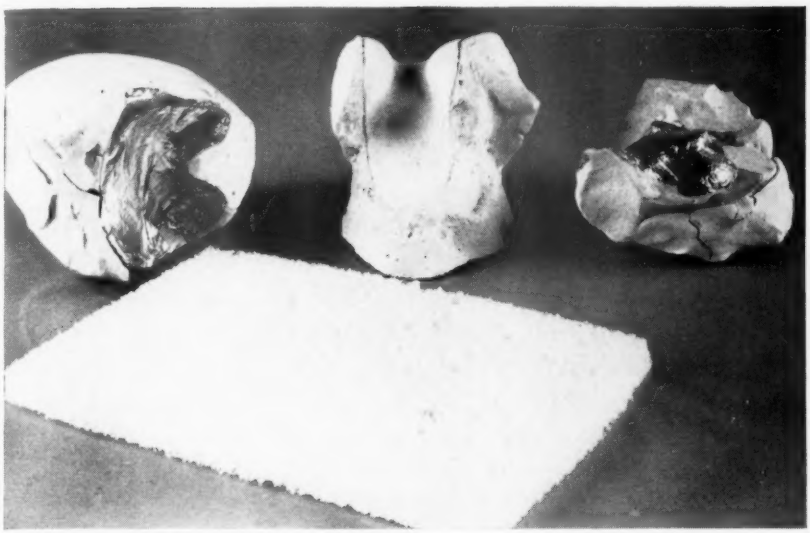


Fig. 1.—The 3-piece die, disassembled, together with a 2 to 3 mm. slice of Ivalon sponge. The center section of the die ("positive") has an outline of the final contour of the prosthesis. The contact surfaces of the two halves of the counterdie ("negative") have been covered with silver foil.

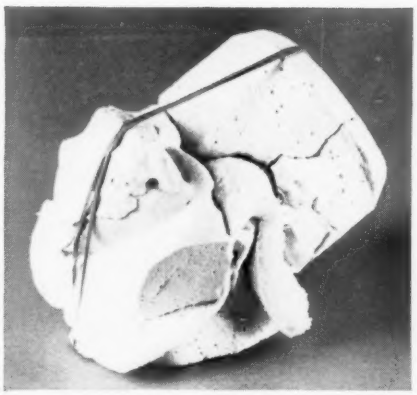


Fig. 2.—After assembly of the die, with the Ivalon sponge slice included, compression is maintained by several encircling rubber bands. The whole assembly is then immersed in boiling water for 10 to 15 minutes, then cooled in running water for an equal period.

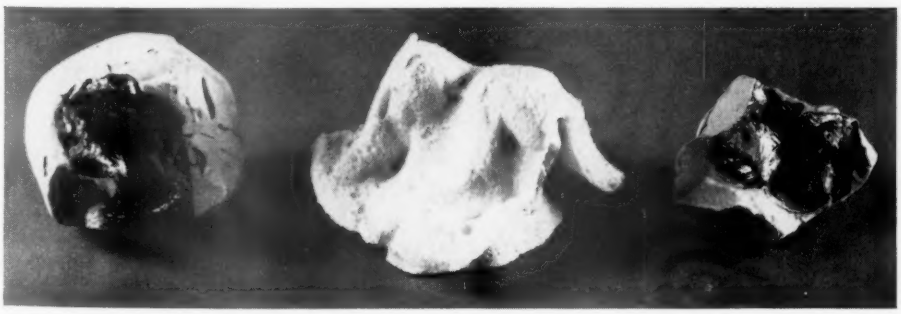


Fig. 3.—The untrimmed prosthesis with die disassembled.

interorificial distance which might be encountered. The flap which diverts the coronary sinus flow is intentionally formed oversize and may be cut away to fit individual needs.

Actual measurement of the volumes of the two newly partitioned chambers reveals that the division by the prosthesis is almost exactly equal; in one instance, left and right atrial volumes were respectively 19 c.c. (52 per cent) and 17 c.c. (48 per cent) of the total common atrial volume.

Fig. 4.—Two views of the trimmed prosthesis in place on the die. Note that in this case the prosthesis has been trimmed to smaller dimensions than the possible maximum.

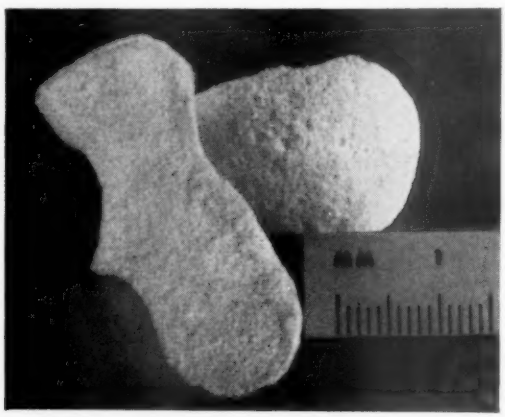


Fig. 5.—Anterior view of the finished prosthesis. Compare this photograph to Fig. 6.

In order to facilitate an understanding of the placement and dimensional relationships of the prosthesis and atria, examples of the pathologic and corrected cardiac circulations are diagrammed in Figs. 6 and 7.

Operative Procedure.—A transternal approach is made through the left third and right fourth intercostal spaces. After the pericardium is opened and the diagnosis confirmed, pressures are measured in both ventricles, the aorta, and pulmonary artery. These measurements are important in establishing the presence or absence of infundibular stenosis. Attention then is directed

to the ductus area. No attempt is made to determine whether or not it is actually patent. Sufficient dissection is carried out to encircle the patent ductus or ligamentum so that it can be occluded during by-pass. After heparinization and cannulation of the left subclavian artery, cannulation of the superior and inferior venae cavae is carried out. For the ordinary by-pass procedure, the

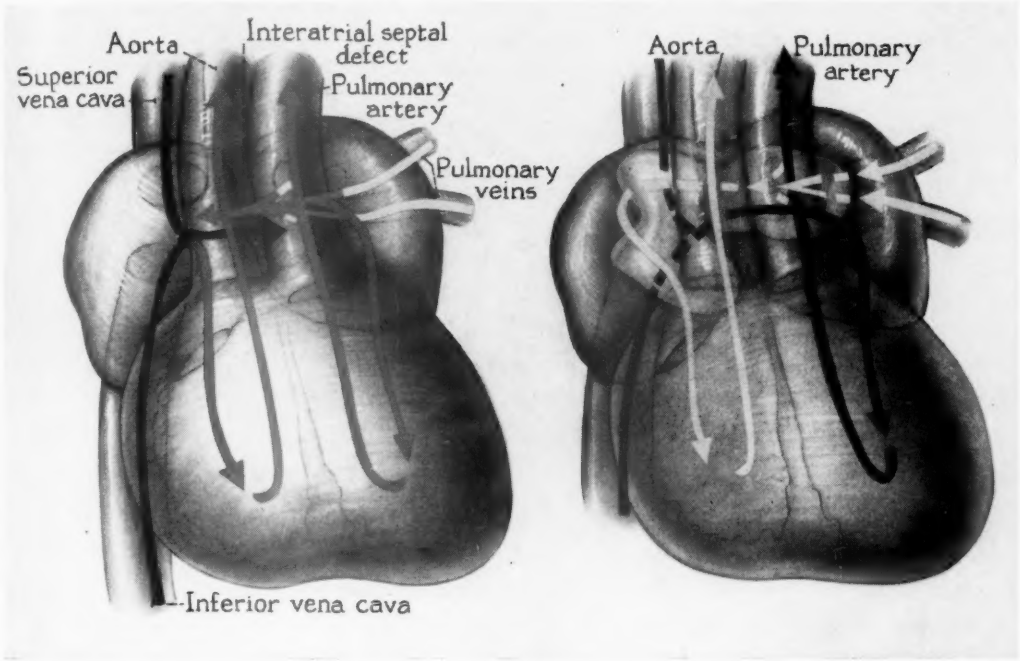


Fig. 6.—Phantom diagrams of the pathologic and corrected circulatory pathways through the heart. On the left is shown transposition with compensation through an interatrial septal defect. On the right interatrial venous transposition has been accomplished by placement of the prosthetic septum. Arrows indicate the changes in flow which result in a completed correction and functional closure of the interatrial septal defect.

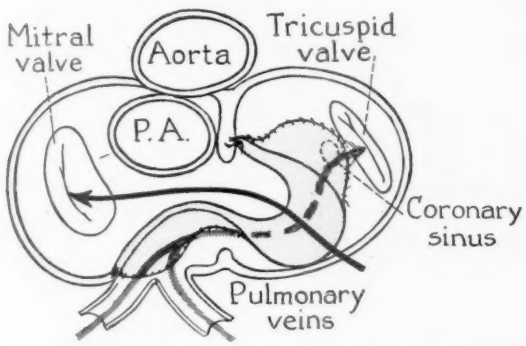


Fig. 7.—A coronal diagram of the prosthesis with final flow pathways indicated by arrows. Note the complete diversion of pulmonary venous and systemic venous blood into right and left atria and ventricles, respectively.

cavae are cannulated through the right atrium. In the operation herein described, the superior vena caval catheter is inserted through the azygos vein so that the orifice of the superior vena cava is unencumbered by the presence of the catheter. The inferior vena caval catheter is inserted in the usual fashion through the inferior wall of the atrium.

Following cannulation of the proper vessels and occlusion of the ductus or ligamentum, the patient's circulation is placed on by-pass. When the situation is stabilized with adequate flow, the heart is arrested by potassium citrate in the usual fashion. A right atriotomy is made and the cardiac interior explored to ascertain the presence of interatrial and/or interventricular septal defects. If an atrial septal defect is present, it is enlarged to maximum by complete excision of the septal wall in all diameters. In the absence of an atrial septal defect, one is created by total excision of the septum. Care is taken to avoid the atrioventricular node in both circumstances. The interior of the left atrium now is inspected and the orifices of all pulmonary veins established. The prosthesis then is sutured in place first compartmentalizing the pulmonary venous flow into the right atrium via the defect in the interatrial septum. Upon completion of the insertion of the prosthesis, the superior and inferior vena caval orifices together with the coronary sinus ostia are directed into the left atrium. Running 4-0 arterial sutures are used. When this bidirectional reversal of all venous flow has been accomplished, total venous transposition has been completed. The interatrial septal defect, whether present or created, has been functionally closed in the process. The end result is corrected transposition.

Additional Considerations.—

Surgical approach: The operative procedure described can be performed entirely through the right chest. Because of the frequent association of patent ductus arteriosus, however, it is imperative that a bilateral thoracotomy be performed in order to occlude the ductus or ligamentum during by-pass. Because dissection about the ductus or ligamentum is necessary for occlusion during by-pass, one might be tempted simply to ligate this structure following by-pass. Our present philosophy has been one of conservatism in this regard, preferring to leave this structure intact (see Discussion).

Cannulation: It is apparent that the internal orifices of the superior and inferior venae cavae can be sutured most easily to the prosthesis if the catheters can be inserted into the cavae themselves. The azygos vein lends itself to ready cannulation of the superior vena cava; however, an insufficient length of the inferior vena cava exists above the diaphragm to do this readily. With insertion of the inferior caval catheter via the right atrium, the running suture must be terminated when the catheter is reached. Two to three interrupted sutures are passed through the external wall of the inferior vena cava picking up the edge of the prosthesis within the heart; the suture is then passed back through the inferior vena caval wall. The two ends are tagged and cannot be tied until the inferior cava is decannulated. The knots will be on the external caval surface. This is a minor disadvantage but might be remedied by dissecting through the diaphragm exposing slightly more cava so that direct caval insertion could be made more safely. Another possibility is the attachment of a cloth tunnel low on the inferior vena cava through which the catheter could be passed or inserting the inferior caval catheter via the femoral vein into the abdominal inferior vena cava.

Coronary sinus: It would seem ideal to direct the blood returning to the heart via the coronary sinus into the left atrium. In the first patient this was done; however, there was some concern that the angle of the prosthesis with the sinus, which, while immediately satisfactory, might become critical with the development of some thrombus on the prosthesis opposite the opening. As there was inadequate time for readjustment of the mold between the cases to be presented, the coronary ostium was excluded from diversion to the left atrium in the second case. In addition, suturing inferior to the ostium could result inadvertently in impaling the atrioventricular node. Since the second case, the mold has been altered so that the compartment in this area will be more capacious. An additional maneuver to incise the ostium in order to enlarge it and thus negate the importance of the angle is another possibility worthy of mention. These considerations have not altered our original concept of management, namely, the complete conversion to the corrected status. In future cases the coronary sinus blood will be directed to the left atrium with the caval blood.

CASE REPORTS

CASE 1.—C. T., a 6½-year-old white girl, had been cyanotic since birth. An acute febrile illness at 15 months was complicated by the development of a spastic right hemiplegia which persisted. At the age of 6 years the child underwent cardiac catheterization. The results were confusing but were thought to be most consistent with total anomalous pulmonary venous drainage and an interatrial septal defect, although it was not possible to catheterize either the pulmonary artery or the aorta. A partial correction of the anomalous pulmonary venous drainage was considered possible and the child was explored. At operation, complete transposition of the great vessels with a large interatrial septal defect was found and nothing further was done.

On March 20, 1957, she was again operated upon, utilizing a pump-oxygenator. Pressure recordings in both ventricles, aorta, and pulmonary artery were not remarkable. With total cardiopulmonary by-pass, 45 c.c. per kilogram per minute, and potassium citrate arrest, the right atrium was widely incised, the interatrial septal defect was enlarged by excision, and the Ivalon prosthesis inserted. The heart was resuscitated after 49 minutes of arrest, but it was soon determined that only the pulmonary veins from the right lung had been shunted by the prosthesis. Therefore, the heart was again arrested with potassium citrate, the atrium reopened, and this error corrected. All caval and coronary sinus blood was diverted to the left atrium and all pulmonary venous blood into the right atrium. The second period of arrest lasted 20 minutes. The total period of by-pass was 105 minutes, total cardiotomy time 76 minutes, and total arrest time 69 minutes. The oxygen saturation in the aorta prior to correction was 60 vol. per cent, following correction 100 vol. per cent.

When the aorta clamp was released the second time, the heart beat well for a few minutes but not as forcefully as previously. The heart then fibrillated. A normal rhythm was restored with the aid of partial by-pass, and in spite of repeated attempts eventually the heart could not be defibrillated.

Comment: Upon opening the left side of the original transternal incision, a sizeable tear was accidentally made in the left ventricle which was adherent to the anterior thoracic wall. Firm pressure controlled this area until the entire incision could be completed. The tear then was sutured satisfactorily. What ill effect the damaged left ventricle may have had in the outcome is problematical.

The failure to compartmentalize all pulmonary venous orifices of the lungs during the first period of arrest was a straightforward error. This necessitated the second elective arrest. It was the operator's impression that the heartbeat was never as forceful following the second resuscitation.

The oxygen saturation of the aortic blood indicated the status of corrected transposition did in fact exist at the completion of cardiac closure.

CASE 2.—P. T., a 6-year-old white girl, had been cyanotic since birth and so retarded in general development that she did not walk until 2½ years of age. A diagnosis of transposition of the great vessels was proposed at the age of 5 and confirmed in April, 1956, by cardiac catheterization. At that time it was noted that the catheter could be passed directly from the right atrium to the right ventricle and thence into the aorta. Gas analyses were consistent with the diagnosis. However, the diagnosis of tetralogy could not be excluded. In February, 1957, repeat studies and angiocardiography confirmed the diagnosis of complete transposition of the aorta and pulmonary artery. The hematocrit was 71.

A bilateral transternal thoracotomy was performed on March 28, 1957. A moderate-sized patent ductus arteriosus was present. Blind digital exploration of the heart chambers revealed intact interatrial and interventricular septa. All venous structures were of normal location and configuration. Pressures taken in both ventricles, aorta, and pulmonary artery were not remarkable.

The left subclavian artery and venae cavae were cannulated and total heart-lung by-pass was begun with a perfusion rate of 55 c.c. per kilogram per minute. Following induced cardiac arrest (total potassium citrate dosage of 1.2 Gm.) the right atrium was opened, and the interatrial septum excised. The Ivalon prosthesis was sutured in place as described; an excellent fit was achieved. The total period of cardiopulmonary by-pass was 38 minutes, open cardiotomy 31 minutes, and cardiac arrest 29 minutes. Following chest closure, the patient recovered well from anesthesia with a normal arterial and venous pressure. By the third hour postoperatively the child was alert, talking, and without neurologic abnormality and was returned to her room. A short time later, the patient turned upon her right side and suddenly became apneic.

The heart continued to beat regularly. Mouth-to-mouth breathing was initiated until an oxygen tank was available. An oxygen mask was applied. Several minutes later the heart developed bradycardia, characteristic of asphyxia, and went into arrest. The chest was reopened and after the usual resuscitative methods a good beat was obtained. The trachea in the meantime was intubated. The heart maintained regular rhythm with maintenance of an adequate blood pressure. However, at no time subsequently did the child make any attempt to breathe spontaneously. Five hours later, all attempts to support the patient were discontinued in spite of an enfeebled, regular heartbeat. The child was pronounced dead 8 hours postoperatively.

At autopsy, numerous air bubbles were found trapped in the cerebral veins. A cardiac finding not appreciated at surgery was a small interventricular septal defect in the outflow tract of the right ventricle. One could with difficulty force the small finger through the opening into the left ventricle. The Ivalon prosthesis was in perfect alignment and anatomically transposed the venous return with the exception of the coronary sinus. This was intentional. (See section on coronary sinus.)

Comment: The short period of elective cardiac arrest of 29 minutes indicates that the prosthesis can be inserted readily and accurately within a reasonable period of time. The total recovery of the patient was excellent in all respects; the respiratory arrest undoubtedly was due to cerebral air embolization. As noted above, the small interventricular septal defect was missed by blind digital exploration prior to atriotomy. Because the defect was in the outflow tract it is difficult to carefully explore this area because of the angle of the finger when introduced through the right atrial appendage. In addition, the defect was deep in a crevice between two thickened papillary muscle bundles, which felt not unlike others within the ventricle. On direct inspection, the defect was hidden under the septal cusp of the tricuspid valve. This unrecognized defect undoubtedly was indirectly responsible for this child's unfortunate death.

The usual methods were carried out to avoid trapping air in the cardiac chambers and when the heart was resuscitated after arrest, the operator was certain that no air was trapped in the right ventricle. Because the right ventricle remains the systemic chamber,

this was particularly important. Small amounts of trapped air in the left ventricle are relatively unimportant as this blood is being propelled to the lungs. Because of the certainty that the right ventricle was free of air on closure, one can only speculate that trapped left ventricular air traversed the septal defect to enter the right ventricle and then the systemic circulation.

DISCUSSION

In order for infants and children with complete transposition to survive after birth, some left-to-right shunt must, of necessity, exist. These associated defects in uncomplicated transposition almost exclusively are interatrial, patent ductus arteriosus, and interventricular, in order of their frequency. They may exist alone or in any combination of two or all three together. It has been pointed out how remarkably small such defects may be and still support life. The most common combination is patent ductus with interatrial septal defect. Most interventricular septal defects are small and in a normal setting may not produce serious hemodynamic difficulties of themselves.

If an interatrial septal defect is the only lesion, then by interatrial venous transposition, the correction of the transposition and the associated defect is complete. In patients with interatrial septal defect and patent ductus arteriosus, only the patent ductus remains to be divided. At present, it does not appear advisable to correct the patent ductus at the same operation. It can be divided and ligated at a later date, an extracardiac procedure. Also, it seems unwise to attempt correction of an interventricular septal defect with or without the other two commonly associated defects. As previously indicated, interventricular septal defects may be small and relatively unimportant. Conditioned by the subsequent course of the patient, intracardiac correction could be done at a later date.

Conservatism regarding the simultaneous treatment of associated defects, other than interatrial, stems from the following consideration. In the first place, the transternal approach seems inadequate to divide safely a patent ductus. Concerning the interventricular septal defect, the approach is best made through the right ventricle. As the right ventricle remains the work chamber generating systemic pressure, it would appear unwise to traumatize the systemic chamber at this time and possibly negate an otherwise successful result. In addition to these valid reasons, another factor is perhaps of even greater importance, namely, the necessity of preserving the opportunity for balancing the two sides of the heart.[8] Because of the associated defects, independent circulations exist in complete transposition. The sudden conversion of transposition to its corrected form with closure of all associated defects might lead to an imbalance of volume and work load between the right and left side of the heart. In our present state of knowledge, it is impossible to predict in individual cases the effect of these independent circulations due to the associated defects. Consequently, it would appear reasonable to leave undisturbed any associated patent ductus and interventricular septal defects so that the opportunity of balancing the two sides of the heart is present during the period of circulatory readjustment. Subsequent developments may alter this conservative approach; however, it is not difficult to visualize, even now, situations where

exceptions may be made to this philosophy. For example, if patent ductus and interventricular septal defects coexisted, perhaps only one, if of sufficient size, need be left for balancing. In this situation, ligation of the ductus at the initial operation might be safely carried out. Also, if one could be certain that the venous transposition was immediately complete and pressure measurements prior to insertion of the prosthesis were favorable, perhaps the ventricular defect could be corrected as well. However, Ivalon compressed to the ratio utilized allows flow through its interstices for an indefinite period. Reversal of flow may not be complete until the clotting mechanism has returned to normal. Thus, imbalances may not be manifest during the operation itself. Until more information is available, conservatism seems indicated regarding the associated defects.

In view of the fact that mainly infants and small children will be operated upon, a question arises concerning the eventual behavior of such a prosthesis in the growing heart. Ivalon itself is well tolerated by human tissue and the tissues of experimental animals in short-term studies and is not the major concern here. The question to be answered in the event of successful placement of the prosthesis is whether the channels created will in time become relatively too small and unable to handle the flows involved. While this is obviously unanswerable for several reasons, it is not likely that a late problem will be created. In the first place, the prosthesis is oversized. In addition, it is not sutured to the true vessel orifices encountered within the heart. Actually, the pulmonary veins all empty into a single compartment. Without increase in size of the prosthesis, that portion of the compartment made up of left posterior atrial wall can increase in size commensurate with the need. Likewise, the anastomosis of the prosthesis to the orifices of the cavae is in part made to atrial wall, and the actual orifice created for the diversion of flow is far greater than the actual size of the cava. Furthermore, if the atrial defect created is adequate to begin with, it is difficult to believe that its size will not become larger if the proper stress is present for enlargement. If the same principles of flow and pressure obtain for the venous as well as arterial vessels, approximately a 70 per cent constriction of channel must take place before an impediment to flow and an increase in back pressure results. Such a reduction in channel size would be difficult to envision. Furthermore, though many of these patients may be infants, the heart itself is not small in transposition. Although the question remains unanswered, the development of late complications of this type appears unlikely.

The successful completion of this operation in both patients indicates that it is a feasible approach for complete transposition. The immediate survival of Case 2 further strengthens our belief that interatrial venous transposition is rational. Although air embolization from presumed trapped intracardiac air, in the presence of an undiagnosed small interventricular septal defect, resulted in a respiratory death, this result does not invalidate the correctness of approach. These two experiences have strengthened our resolve to persist in

efforts along identical lines. The correction of transposition as well as its associated defects appear to be simplified by the operative approach which is described.

SUMMARY AND CONCLUSIONS

1. A one-stage intracardiac operation for the conversion of complete transposition of the aorta and pulmonary artery to corrected transposition is described.

2. Two cases are presented in which this procedure was utilized for the first time. One child survived only to die of a respiratory arrest secondary to cerebral air embolism presumably from air trapped within the heart.

3. The rationale concerning the management of the commonly associated defects is presented. The correction of transposition as well as its associated defects is simplified by the operative procedure presented.

4. The advantages of interatrial venous transposition have been stressed as well as the disadvantages of the multiple extracardiac maneuvers used to effect the same physiologic state.

We gratefully wish to acknowledge the valuable technical assistance of Dr. Oscar E. Beder of the School of Dentistry, University of Washington, in the preparation of the prosthesis mold.

REFERENCES

1. Baffes, T. G.: A New Method for Surgical Correction of Transposition of the Aorta and Pulmonary Artery, Surg., Gynec. & Obst. **102**: 227-233, 1956.
2. Bailey, C. P., Cookson, B. A., Downing, D. F., and Neptune, W. B.: Cardiac Surgery Under Hypothermia, J. Thoracic Surg. **27**: 73-91, 1954.
3. Björk, V. O., and Bouckaert, L.: Complete Transposition of the Aorta and Pulmonary Artery. An Experimental Study of the Surgical Possibilities for Its Treatment, J. Thoracic Surg. **28**: 632-635, 1954.
4. Blalock, A., and Hanlon, C. R.: The Surgical Treatment of Complete Transposition of the Aorta and the Pulmonary Artery, Surg., Gynec. & Obst. **90**: 1-15, 1950.
5. Graanboom: Quoted by Lillehei, C. W., and Varco, R. L.[9]
6. Hanlon, C. R., and Blalock, A.: Complete Transposition of the Aorta and Pulmonary Arteries. Experimental Observations on Venous Shunts as Corrective Procedures, Ann. Surg. **127**: 385-397, 1948.
7. Jesseph, J. E., Herron, P. W., and Merendino, K. A.: Unpublished data.
8. Kay, E. B., and Cross, F. S.: Surgical Treatment of Transposition of the Great Vessels, SURGERY **38**: 712-716, 1955.
9. Lillehei, C. W., and Varco, R. L.: Certain Physiologic, Pathologic, and Surgical Features of Complete Transposition of the Great Vessels, SURGERY **34**: 376, 399, 1953.
10. Murphy, T. O., Gott, V., Lillehei, C. W., and Varco, R. L.: The Results of Surgical Palliation in 32 Patients With Transposition of the Great Vessels, Surg., Gynec. & Obst. **101**: 541-544, 1955.
11. Mustard, W. T., Chute, A. L., Keith, J. D., Sirek, A., Rowe, R. D., and Vlad, P.: The Surgical Approach to Transposition of the Great Vessels With Extracorporeal Circuit, SURGERY **36**: 39-51, 1954.

STUDIES IN THE HEALING OF LARGE RIGHT VENTRICULOTOMIES

W. Dean Warren, A.B., M.D.,* Frank S. Blanton, Jr., B.S., M.D.,** and William H. Muller, Jr., B.S., M.D.,*** Charlottesville, Va.

(From the Department of Surgery, University of Virginia School of Medicine)

FURTHER developments and refinements of extracorporeal heart-lung systems have made possible the correction of intracardiac defects which heretofore were not considered amenable to corrective surgery. Wounds in actively and forcefully contracting muscle subject to high pressure make the ultimate fate of ventriculotomies a problem.[1] It seemed timely, therefore, to investigate by various techniques certain aspects of healing of large ventricular wounds.

Previous work on heart wounds has been largely confined to evaluation of techniques in management of traumatic wounds of the myocardium. It has long been known that the regenerative power of cardiac muscle tissue is insignificant and that healing takes place by the formation of fibrous scar. This experiment was not designed to study the techniques of ventriculotomy closure but rather to evaluate the strength of the scar and its effect on the gross activity of the heart, on the conduction mechanism, and on the vascular supply to the surrounding myocardium.

METHODS

Twenty mongrel dogs weighing 14 to 18 Kg. were used. Intravenous Nembutal (12 mg. per pound) was employed for anesthesia. In 2 animals, the cardiotomy was performed without interrupting the circulation. The left pleural cavity was entered through the fourth intercostal space and the heart exposed through a large incision in the pericardium. A suture was placed in the mid-portion of the right ventricle and traction was applied to "tent" the right ventricular wall. A large portion of the right ventricular wall was grasped with a curved noncrushing vascular clamp, and a longitudinal incision 3 to 4 cm. in length was made through the full thickness of the wall. The edges of the wound were approximated with a continuous 3-0 atraumatic silk suture which passed through the full thickness of the ventricular wall with stitches placed approximately 3 mm. apart and 3 to 4 mm. from the cut edge. The pericardium was closed with interrupted silk sutures and the chest closed in the routine fashion. Eighteen animals were explored through the right fourth

Supported by U. S. Public Health Grant No. 2308.
Received for publication Feb. 19, 1957.
*Assistant Professor of Surgery, University of Virginia School of Medicine.
**Fellow in Surgery, University of Virginia School of Medicine.
***Professor and Chairman, Department of Surgery, University of Virginia School of Medicine.

intercostal space and were perfused with a heart-lung system. Incisions measuring 5 to 6 cm. in length were placed in the mid-portion of the right ventricle without the use of the vascular clamp and without regard to the vascular pattern. The wound closure was accomplished as previously described. To increase the right ventricular pressure and place the wounds under greater stress, pulmonary artery stenosis was created in 5 animals at intervals ranging from 2½ to 8 weeks following ventriculotomy. This was accomplished by application of a partial occlusion clamp and excision of a segment of the vessel wall; the constricted area was wrapped with a band of reactive polyethylene film and cotton tape as described by Muller and Dammann.[8] The degree of the stenosis was evaluated by the presence of a thrill over the area and by pressure changes in the right ventricle and pulmonary artery.

Penicillin, 600,000 units, given at the conclusion of each procedure, was repeated daily if indicated.

The dogs were sacrificed at intervals ranging from 2 to 16 months except for one animal that expired after 2½ weeks, and the following studies were performed.

1. Electrocardiographic studies were obtained under Nembutal anesthesia before and at intervals following the ventriculotomies.

2. Immediately prior to sacrifice, a right thoracotomy was performed and observations of heart structure and action were made before and after opening the pericardium. Animals with artificially created pulmonary stenosis were re-evaluated by pressure changes in the right ventricle and pulmonary artery by the presence of a thrill over the area, by the gross changes in the right ventricle, and by electrocardiographic evidence of right axis deviation.

3. Upon removal of the heart, the epicardial and endocardial surfaces of all the chambers were carefully examined for changes in appearance, adhesive pericarditis, and adherent clots. The thickness of the myocardium in the region of the scar and elsewhere was noted. Specimens of the scar and surrounding myocardium were taken for histologic study.

4. In several animals, the right ventricle was distended with fluid in an attempt to measure the pressure necessary to disrupt the wound.

5. Strips of myocardium, cut transversely through the cardiotomy scar and measuring 1 cm. in width with approximately 1.5 to 2 cm. of myocardium on each side of the scar, were tested for disruptive strength. Two plastic pinch clamps were devised to grasp the ends of the strips of myocardium. The plastic jaws were grooved to promote a firmer grip and were firmly approximated by means of a screw. As added assurance that the specimen would not slip, the jaws were perforated so that 4 or 5 pins could be passed through the holes impaling the specimen. These clamps were provided with hooks so that one could be fastened to a stationary crossbar and a fluid receptacle weighing 350 Gm. suspended from the other. By adding distilled water to the receptacle at a constant rate of 1,200 c.c. per minute until the specimen parted, the weakest area in the specimen was located and the relative tensile strength of the

area was determined by adding the weight of the water to the weight of the receptacle. In each case, the myocardial strips used were completely traversed by scar, and duplicate strips were taken and an average obtained.

6. The hearts of 6 normal dogs were also studied by microscopic section through the portion of the right ventricle that was traversed by the cardiotomy in the dogs operated upon and by tension studies of myocardium in that area using the gravity flow method described above.

RESULTS

The electrocardiographic examinations were, for the most part, within normal limits. Two dogs showed evidence of myocardial ischemia due probably to the anesthesia. In none of the dogs with myocardial thinning and fibrosis was there an abnormal tracing. There was right axis deviation in one dog with pulmonary artery stenosis. The others in this group were essentially normal.

At thoracotomy, some degree of adhesive pericarditis was evident in all the animals. However, there were no discernible changes in heart size, contour, or action. None showed ventricular aneurysms. On opening the pericardium the adhesions were limited to the immediate area of the scar and, in most instances, were quite dense and strong. In cases in which the clamp was applied to the myocardium, there was scarring through the full thickness of the wall at the site of application. There were no thrombi present on the endocardial surface of the right ventricle. The wounds and sutures in all dogs were found to be well endothelialized (Fig. 1). Marked tissue reaction around the sutures was grossly evident in 3 dogs, but no abscesses could be identified.

Of important significance were areas of myocardial thinning between the wound and the anterior descending branch of the left coronary artery in 6 animals (Figs. 2 and 3). Fig. 4 shows the quite constant vascular pattern of the right ventricle in the dog's heart. The incisions were placed in midventricle without regard to the location of the branches of the coronary arteries. Thinning of the wall occurred when the incisions were placed closer to the right coronary artery and cut across the larger descending branches of this vessel. These areas varied in size from 2.5 by 1.5 cm. to 0.8 by 0.4 cm. and appeared to be composed entirely of fibrous tissue which was sufficiently thin to be readily translucent in all cases, and indeed, almost transparent in 2.

In 2 animals the spetal leaflet of the tricuspid valve was noted to be markedly swollen and succulent, measuring approximately 5 mm. in thickness at its margin (Fig. 2). These changes occurred in none of the dogs with pulmonary artery stenosis.

Pulmonary stenosis adequate to increase significantly the strain on the right ventricle was present in 3 of the 5 dogs on which it was attempted. There were significant pressure changes and a thrill over the pulmonary artery at the final thoracotomy. In the one animal in which there was electrocardiographic evidence of right axis deviation, there was marked right ventricular hypertrophy. In none of this group, however, was there any change in wound healing. Myocardial thinning occurred in one of the animals of this group and was due to location of the incision as in the dogs with normal right ventricular

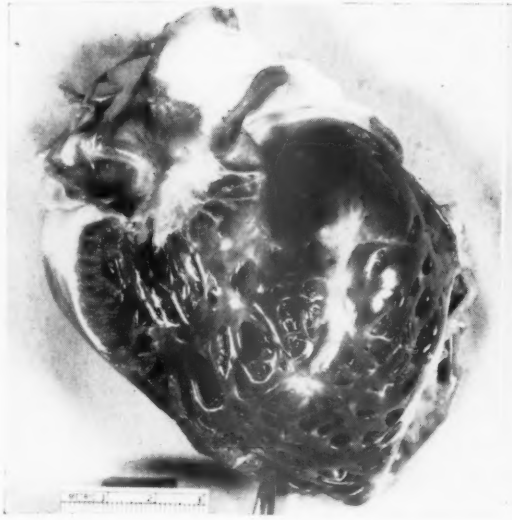


Fig. 1.

Fig. 2.

Fig. 1.—Well-healed cardiotomy scar viewed from inside the right ventricle.
Fig. 2.—Interior of the right ventricle showing the area of myocardial fibrosis and thinning indicated by the pointer. The healed cardiotomy is visible just above this area.

Fig. 3.

Fig. 4.

Fig. 3.—View of a right ventricular wall showing changes similar to Fig. 2 but photographed with the light source behind the ventricle to demonstrate the thinning and translucence of the area. The sutures are clearly visible.
Fig. 4.—Superficial vascular pattern of the right ventricle in the dog.

pressure. The electrocardiogram in this animal was normal, and the right ventricular pressure increase was less marked than in the dog that showed electrocardiographic changes and gross right ventricular hypertrophy.

Fig. 5.

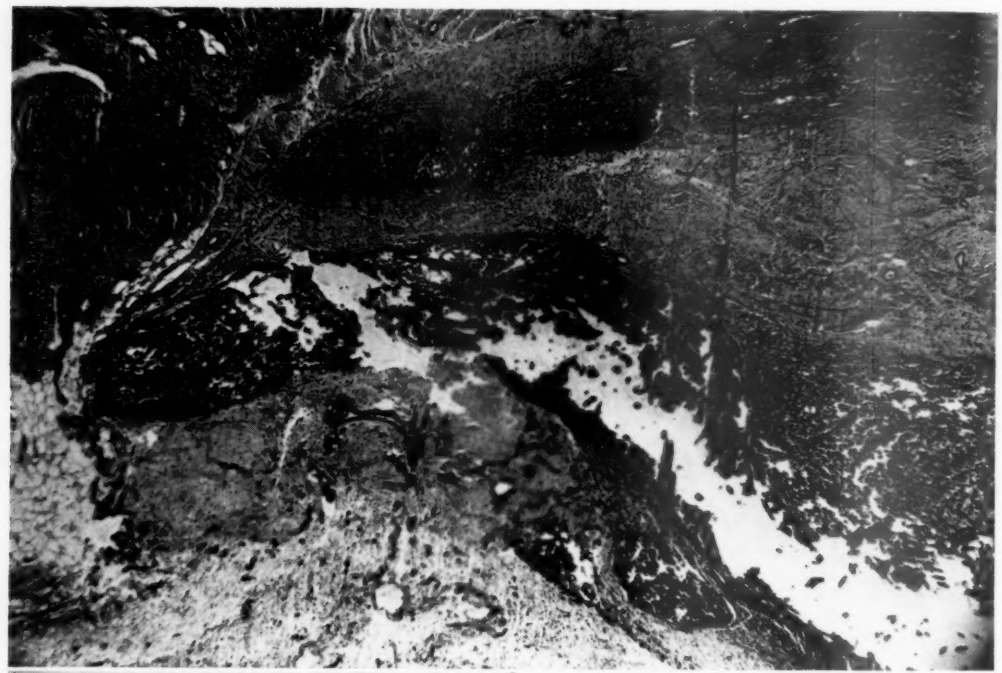


Fig. 6.

Fig. 5.—Photomicrograph showing marked chronic inflammatory reaction around a silk suture.

Fig. 6.—Photomicrograph showing the myocardial thinning in cross section.

Healing was characterized by dense collagen originating at the side of the wound and extending into the surrounding tissues. An unexpected finding in 6 dogs was a severe chronic inflammatory response with infiltration of lymphocytes, plasma cells, and early foreign body giant cells around the silk sutures, extending through the full thickness of the myocardium (Fig. 5). Cultures had not been taken but MacCallum stains revealed no bacteria. This picture was felt to be due to reaction to the preserving fluid contained in some of the suture vials. In one animal inflammation about the sutures was very severe even though the operation had been performed 10 months previously.

Except for a few scattered bundles of myocardium, the thinned areas in the ventricular wall consisted of fibrous tissue which appeared to originate from the epicardium and endocardium and was accompanied by considerable fat infiltration (Fig. 6). Of considerable interest was the pronounced trauma to the myocardium produced by the so-called noncrushing vascular clamp. The area of the ventricular wall which lay directly in the grasp of the clamp showed complete replacement of myocardium by fibrous tissue. However, the myocardium, which had been completely encircled by this thin line of full-thickness scar, seemed entirely normal (Fig. 7).

Fig. 7.—Elliptical scar produced by noncrushing vascular clamp, traversed by cardiotomy scar.

Efforts to study the strength of the healed cardiotomy by distending the right ventricle were unsatisfactory. In several hearts a catheter was threaded through the pulmonary artery, all other vessels were occluded with clamps, and the right ventricle was distended with fluid. Heart valves became incompetent or the occluded vessels ruptured, but the ventricular scar remained intact although an intraventricular pressure of over 240 mm. Hg was reached in 2 hearts. Accordingly, this method was abandoned. The remainder of the wounds were tested by the gravity flow method described above, unless the cardiotomy was placed so close to the septum that this was not possible. In no instance did the healed wounds disrupt. In every instance, including 5

hearts with gross thinning adjacent to the wound, the site of disruption was in normal myocardium or at the point of attachment of the myocardial strips despite special precautions taken when attaching the strips to the tension sources.

In these studies, an average tension of 1,650 Gm. was tolerated before myocardial disruption occurred. In the 12 hearts tested, the range was from 900 to 2,400 Gm. The 6 hearts with myocardial thinning tolerated an average of 1,670 Gm. with a range from 1,550 to 2,000 Gm. In the 6 normal dogs tested, the average tension at disruption was 1,645 Gm. with a range from 1,350 to 1,900 Gm. The strips showing marked inflammation at the scar resisted an average tension of 1,610 Gm. with a range of 1,010 to 1,900 Gm. The strips from hearts on which the vascular clamps were used parted at an average tension of 2,275 Gm. with a range from 1,900 to 2,650 Gm. In the latter case, the strips did not tear through the area of myocardium encircled by scar.

DISCUSSION

Possibly the most significant observation in this study was the myocardial infarct which consistently resulted from placing the cardiotomy incision across the branches of the right coronary artery which supply most of the wall of the right ventricle. It would seem that in the dog one should be careful to place a right ventricular incision between the ends of the right coronary branches and the branches of the anterior descending limb of the left coronary (Fig. 4). This vascular arrangement, although remarkably common in the dog, is not the most frequent one seen in the human heart. The general pattern of distribution of the coronary arteries and their branches in man is not constant, but there are 3 major arrangements[5]: (1) Predominant right coronary occurring in 50 per cent of the cases in which the right coronary artery supplies all of the wall of the right ventricle, the posterior half of the interventricular septum and a large part of the posterior wall of the left ventricle, (2) balanced coronaries occurring in 30 per cent of the cases and in which the right coronary again supplies the right ventricle and the posterior half of the interventricular septum, and (3) the dominant left coronary occurring in 20 per cent and being the arrangement seen in the dog. In this group, the left coronary branches extend across the interventricular septum anteriorly and supply a portion of the anterior wall of the right ventricle.

Thus, in only 20 per cent of human hearts is there an area away from the interventricular septum where one may incise the right ventricle knowing there is excellent blood supply to both sides of the wound.

Although the thinned areas seem stronger than normal myocardium in the tension studies, it seems possible that aneurysmal bulging of the area might be a later consideration. A review of the literature on cardiac aneurysms reveals that perhaps 9 per cent of all myocardial infarcts later become aneurysms.[9] One series reports the incidence of such aneurysmal dilatation as high as 38 per cent.[7] The consequences and eventual outcome of these aneurysms is disputed. Friedman and White[4] reported on 270

autopsies revealing myocardial infarcts. There were no instances of rupture of old infarcts in which aneurysmal dilatation had occurred, whereas rupture was not infrequently the cause of death in patients with infarcts less than 2 weeks old. This is borne out by Brams and Gropper[2] who reported 21 cases of cardiac aneurysm with no instance of rupture and who feel that these aneurysms are not a menace to life. In 40 cases of cardiac rupture, Hunter and Benson[6] noted only one occurring in a cardiac aneurysm and Fischer,[3] who reported a case of ruptured aneurysm, states that it is exceedingly rare. The factors which are prerequisite to the development of cardiac aneurysm in an old infarct may include magnitude of infarct and inadequacy of bed rest following the infarction.[2] The work of Sutton and Davis[10] in a small series of dogs seems to indicate that the size and thickness of the scar resulting from an experimental infarct depends largely on the amount of bed rest following infarction.

Brams and Gropper[2] and Parkinson, Bedford, and Thompson[9] noted that the majority of cardiac aneurysms developed in normotensive individuals and concluded that hypertension was not a prerequisite. The latter authors postulated that perhaps the thickened wall of a hypertrophied heart, as seen in hypertensives, is less likely to yield when infarcted than is a heart not so thickened. This might indicate that a pre-existing hypertension would tend to preclude aneurysm formation in an infarct, whereas a subsequently developing hypertension might predispose to it. This latter point, however, was not borne out in this experiment since subsequently produced right ventricular hypertension had no effect on the healed wound. Further studies to evaluate the effect of both pre-existing and subsequently created hypertension are now in progress.

The situations in which it becomes necessary to apply a vascular clamp to myocardium are rare, but this is possibly indicated in the treatment of a symptomatic saccular ventricular aneurysm.[7] It may be well to keep in mind the areas of full-thickness replacement of myocardium by fibrous scar that occurred when clamps were applied to the right ventricular wall in this experiment.

In general, this study demonstrates no reduction in the strength of the myocardial wall following right ventriculotomy, nor did the marked inflammatory reaction around the sutures in several cases cause any loss of strength. There have been no cases of incisional breakdown and no gross abnormalities of action or conduction. In this study, there were no demonstrable complications associated with the myocardial thinning which occurred in 6 (30 per cent) of the animals. However, these defects must be considered a potential source of future difficulty probably in direct relation to their size and only perhaps in relation to subsequent development of pulmonary hypertension. This problem may possibly be more acute in the human heart than in the dog because of the vascular arrangement which is predominant in man.

The efficiency of the incised ventricle in the immediate postoperative period has not yet been evaluated. Pulmonary congestion following cardiotomy is far from rare and this added strain on the incised right ventricle

may play a part in producing early ventricular inadequacy and failure. Perhaps more of the postoperative deaths following cardiotomy are due to this factor than is currently realized.

SUMMARY

Right ventriculotomies were performed in 20 dogs and subsequent pulmonary stenosis was produced in 5 (25 per cent) in an attempt to increase right ventricular strain. The animals were sacrificed at intervals ranging from 2 to 16 months, and at that time electrocardiograms and gross observations of the heart and its action were made. The incisions were examined grossly and microscopically, and tension studies were performed on the wound area by a gravity flow method.

There were no cases of incisional breakdown or gross alteration in heart action. Myocardial fibrosis and thinning in 6 animals (30 per cent) occurred between the incision and the branches of the left anterior descending coronary artery when the cardiotomy was placed high on the right ventricle, interrupting the branches of the right coronary artery. This vascular pattern which occurs consistently in dogs is found in only 20 per cent of human hearts. Tension studies revealed no loss of strength of the right ventricular wall, and in no case did disruption occur at the cardiotomy scar or through the area of myocardial thinning. It was noted that so-called noncrushing vascular clamps produced marked full-thickness scarring when applied to myocardium. The problem of cardiac aneurysms is briefly discussed.

REFERENCES

1. Blalock, Alfred: Discussion of paper by Lillihei, C. Walton, Cohen, M., Warden, H. E., Reid, R. C., Aust, J. B., DeWall, R. A., and Varco, R. L.: Direct Vision Intracardiac Surgical Correction of the Tetralogy of Fallot, Pentalogy of Fallot, and Pulmonary Atresia Defects: Report of First Ten Cases, Ann. Surg. **142**: 422, 1955.
2. Brams, W. A., and Gropper, A.: Cardiac Aneurysms, Illinois M. J. **78**: 246, 1940.
3. Fischer, R. L.: Cardiac Aneurysms With Rupture, Am. Heart J. **30**: 133, 1945.
4. Friedman, S., and White, P. D.: Rupture of the Heart in Myocardial Infarction, Ann. Int. Med. **21**: 778, 1944.
5. Gregg, Donald E.: Coronary Circulation in Health and Disease, Philadelphia, 1950, Lea & Febiger, pp. 26, 27.
6. Hunter, W. C., and Benson, R. L.: Rare Form of Saccular Cardiac Aneurysm With Spontaneous Rupture, Am. J. Path. **9**: 593, 1933.
7. Likoff, W. C., and Bailey, C. P.: Ventriculoplasty—Excision of Myocardial Aneurysm, J. A. M. A. **158**: 915, 1955.
8. Muller, William H., Jr., and Dammann, J. Francis, Jr.: The Surgical Significance of Pulmonary Hypertension, Tr. Am. S. A. **70**: 199, 1952.
9. Parkinson, J. B., Bedford, B. E., and Thompson, W. A. R.: Cardiac Aneurysms, Quart. J. Med. **7** (New Series): 455, 1938.
10. Sutton, D. C., and Davis, M. D.: Effects of Exercise on Experimental Cardiac Infarction, Arch. Int. Med. **48**: 1118, 1931.

STUDIES ON THE EFFECT OF HYDROCORTISONE ON IRREVERSIBLE HEMORRHAGIC SHOCK IN THE DOG

ROBERT W. KNAPP, M.D., AND JOHN M. HOWARD, M.D., ATLANTA, GA.

(From the Whitehead Department of Surgery, Emory University School of Medicine, and Grady Memorial Hospital)

THE transfusion of large quantities of whole blood has become an acceptable, efficacious, and in many instances, life-preserving procedure. While adequate transfusion ordinarily relieves hypovolemic crises, there are innumerable instances in which traumatic and postoperative shock fails to respond to replacement of whole blood. Perhaps the most frustrating phase of this problem is the situation in which the patient is encountered who has been in shock for several hours but who fails to respond to the administration of blood in volumes which would appear adequate for replacement. While the blood pressure may improve transiently, it gradually falls, and finally the hypotension becomes refractory to all standard therapy. This problem has come under close scrutiny by many investigators who have attempted experimentally to discover the irreversible changes that take place in prolonged hypotension. The field has been studied in many aspects. Frank, Seligman, and Fine,[3] using cross-circulation technique in dogs, identified the ischemic liver as a dominant shock organ and later indicated the role of "gram negative bacteremia" in the pathogenesis of irreversible shock.[1] Others have attempted to correlate vitamin B_{12} or carbohydrate metabolism with the shock process.[6] As in almost every other phase of disease, the role of the adrenal cortex has not been excluded from this program of investigation. In isolated clinical experiences there have been uncontrolled attempts to employ hydrocortisone in the treatment of post-transfusion hypotension.[5] The apparent response has been encouraging in several instances. In the one clinical series recorded in the literature, Lichtman[7] reported extremely encouraging results. With 24 of his patients who were in shock refractory to intravenous whole blood transfusion, varying regimes of active adrenal steroids were used. Twenty-two patients survived.

Other clinical experience has been less spectacular, but nevertheless from these instances it has become apparent that the adrenocortical hormones might have a beneficial effect on hypotension independent of any direct vasopressor activity. Frank[2] and also Howard and DeBakey[6] failed to demonstrate any improvement in survival of dogs using cortisone alone, but Fine[1] had indicated the value of pretreatment with antibiotics. It was our belief that an evaluation of adrenal hormones should be controlled by having the animals on an antibiotic

Received for publication March 11, 1957.

Supported in part by a United States Public Health Service student fellowship grant and by a grant from the Department of Army (DA 49-007-MD-732).

regime. Thus the goal of this investigation was to standardize a shock preparation including the antibiotic effect and then to demonstrate, using hydrocortisone, the further effect on survival of these dogs over the survival of the control animals.

METHODS AND RESULTS

Healthy, afebrile mongrel dogs were treated with Terramycin* in an oral dosage of 5.0 Gm. daily for 3 days. Under local procaine infiltration and without preoperative sedation, a femoral artery was cannulated and a uniform bore glass cannula was connected to a mercury manometer and a hanging reservoir was adjusted to maintain an arterial pressure of 30 mm. Hg. After recording the original arterial pressure, the animal was allowed to bleed into the hanging reservoir. Under these circumstances he would maintain his pressure at 30 mm. Hg for several hours with minimal fluctuations of the amount of blood lost into the reservoir. Thereafter, his compensatory mechanism would begin to fail and, in order to maintain his pressure at 30 mm. Hg, autotransfusion from the reservoir would begin. When 40 per cent of the blood initially lost into the reservoir was reaccepted, the criteria of irreversibility were met. At this time the animal was rapidly transfused intravenously with the remaining blood in the reservoir to which was added 100 mg. of hydrocortisone.† The duration of hypotension was measured between the time of hemorrhage and the point when 40 per cent of the blood loss had been reaccepted. The blood pressure response to transfusion and the length of survival after transfusion were also recorded. Two basic control studies were done; one in which no medication was given, and another in which the animals received orally the standard dosage of Terramycin, 5.0 Gm. daily for 3 days before hemorrhage. In the latter study, hydrocortisone was omitted. Table I is a comparison of the results in the 3 groups. There were no survivors and no significant variations in the mean shock time, mean survival time, or mean response to transfusion.

TABLE I. EFFECT OF HYDROCORTISONE ON IRREVERSIBLE SHOCK IN DOGS

	MORTALITY	MEAN SHOCK TIME	MEAN SURVIVAL TIME	MEAN BLOOD PRESSURE RESPONSE TO TRANSFUSION
Untreated 6 dogs	100%	4.3 hours	3.3 hours	49 mm. Hg
Terramycin pretreatment 11 dogs	100%	2.7 hours	2.1 hours	39 mm. Hg.
Terramycin pretreatment Hydrocortisone with retransfusion 9 dogs	100%	3.8 hours	3.1 hours	53 mm. Hg.

*Terramycin supplied through courtesy of Charles Pfizer & Co., Inc., Brooklyn 6, N. Y.
†Hydrocortef supplied through courtesy of The Upjohn Company, Kalamazoo, Mich.

DISCUSSION

The administration of hydrocortisone was of no apparent benefit to these animals and did not alter the pattern of shock. The series was small, but the results were so uniform that further study hardly appeared justified. Several investigators have utilized this standard shock preparation, and the control, untreated series confirms their experience as to the anticipated mortality. The negative results, when only Terramycin was used, paralleled the results of Hardy and his associates.[4]

SUMMARY

Utilizing a standard preparation of irreversible hemorrhagic shock in the dog, hydrocortisone was administered with transfusion. No effect of the hydrocortisone could be detected in the survival rate, mean shock time, mean survival time, or mean blood pressure response following transfusion.

REFERENCES

1. Frank, H. A., Jacob, S. W., Schweinburg, F. B., Goddard, J., and Fine, J.: Effectiveness of an Antibiotic in Experimental Hemorrhagic Shock, Am. J. Physiol. **168**: 430, 1952.
2. Frank, H. A., Jacob, S. W., Weizel, H. A., Reiner, L., Cohen, R., and Fine, J.: Effects of ACTH and Cortisone in Experimental Hemorrhagic Shock, Am. J. Physiol. **180**: 282, 1955.
3. Frank, H. A., Seligman, A. M., and Fine, J.: The Prevention of Irreversibility in Hemorrhagic Shock by Viviperfusion of the Liver, J. Clin. Invest. **25**: 22, 1946.
4. Hardy, E. G., Morris, G. C., Yow, E. M., Haynes, B. W., and DeBakey, M. E.: Studies on the Role of Bacteria in Irreversible Hemorrhagic Shock in Dogs, Ann. Surg. **139**: 282, 1954.
5. Howard, J. M.: Unpublished data.
6. Howard, J. M., and DeBakey, M. E.: The Treatment of Hemorrhagic Shock With Cortisone and Vitamin B_{12}, SURGERY **30**: 161, 1951.
7. Lichtman, A. L.: Adrenal Cortical Steroids in Treatment of Surgical Shock, Exper. Med. & Surg. **12**: 434, 1954.

EVALUATION OF THE NEED FOR POROSITY IN SYNTHETIC ARTERIAL PROSTHESES

A Case Report and Evaluation of Dacron Aortic Grafts in Dogs

Graham Knox, M.D., and Charles F. Begg, M.D., New York City, N. Y.

(From the Surgical Service and the Surgical Research Laboratory and the Pathologic Laboratories, St. Luke's Hospital)

THE physical properties of cloth arterial prostheses have been the subject of intensive investigation.[1-3] The purpose of this report is to re-evaluate the importance of porosity. Our interest in this property was initiated by a patient in whom a Dacron* arterial graft was observed over a period of 12 months. We shall also report pertinent findings in a series of dogs in which Dacron sleeves were used to replace segments of the abdominal aorta.

CASE REPORT

Patient L. K. was a 67-year-old man. In July, 1955, an occluded segment of his left femoral artery was replaced with a Dacron prosthesis 31 cm. long and 0.5 cm. in diameter. End-to-end anastomoses with the femoral artery were secured with 5-0 silk sutures. Ischemic symptoms were completely relieved and pulsations reappeared in vessels distal to the graft.

Eight months later, two sinus tracts appeared in the scar. Exploration demonstrated an angulated Dacron sleeve graft which could be seen pulsating in the depths of the sinuses. The texture, weave, and color of the cloth had not changed since its original installation. A thin layer of dense fibrous tissue covered the surface of the tissue in contact with the Dacron but was not adherent to the cloth. The tissue was indurated for a distance of 1 to 2 cm. from the graft and was the site of an intense inflammatory reaction (Fig. 1). The graft was straightened and relocated in the areolar tissue of the thigh away from the indurated tissue. Pulsations distal to the graft remained good before, during, and after the procedure.

Three months later (11 months after the first operation) a sinus tract was again discovered in the wound. Operation revealed the graft pulsating in a bed of granulation tissue which was at no point adherent to the cloth (Fig. 2). The sleeve was now placed in a tunnel in the adductor muscles. Distal pulses remained palpable.

Three weeks later, pain, coldness, and pallor of the foot and calf occurred. The graft was again exposed and found to be occluded with the distal end separated from the artery. *Staphylococcus aureus* was cultured from the wound. The Dacron graft was removed and a homograft used to replace it. This failed to function, and the leg was amputated 13 months after the initial graft procedure.

The Dacron sleeve, removed 12 months after its implantation, was lined with a thin layer of hyalinized fibrous tissue. No endothelium was found. A thin coat of dense fibrous tissue was also present on the outer surface of the tissue adjacent to the cloth, but no tissue of any sort could be found in the interstices of the Dacron (Fig. 3).

Aided in part by grants from the New York Heart Association, The Hartford Foundation, and The Sloan Foundation.

Received for publication Feb. 19, 1957.

*A heavily calendered fabric of taffeta weave with a relatively low porosity. Supplied by Sol Lamport, 350 Broadway, New York City.

EXPERIMENTAL PROCEDURES

Material and Methods.—In each of 20 mongrel dogs, weighing from 40 to 55 pounds, a 4 cm. Dacron sleeve graft was substituted for a segment of the abdominal aorta below the renal arteries. The anastomoses were performed with 5-0 black silk. No special diet or medication was used. The animals were sacrificed for study of the grafts at monthly intervals over a period of 12 months. The graft remained patent in 16 animals.

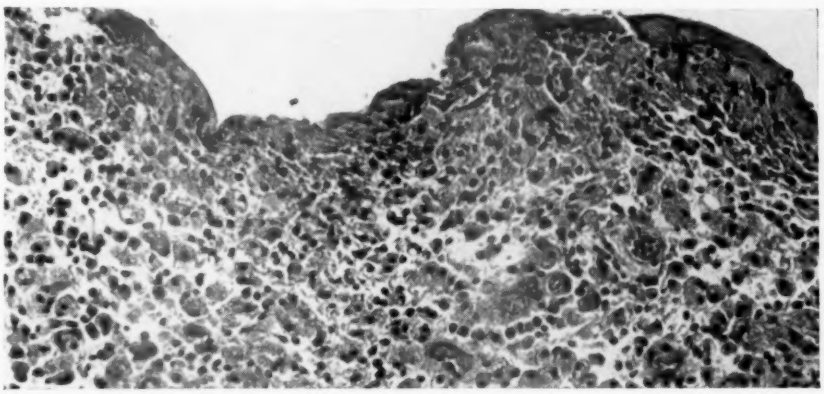


Fig. 1.—Patient L. K., 8 months post graft. Section of tissue adjacent to Dacron graft. Hyalinized fibrous tissue forms a narrow layer on the surface in contact with the cloth; beneath this is granulation tissue heavily infiltrated with lymphocytes and macrophages (H and E, original magnification 500 diameters).

Fig. 2.—Patient L. K., 11 months after installation of Dacron. The graft lies free in the areolar tissue. There is no adhesion of the adjacent tissue to the cloth. Graft is patent and carrying a good pulsatile flow.

Results.—By 10 days, a glistening layer of fibrin had completely covered the inner surface of the cloth (Fig. 4). By the second month this had become a thin, hyalinized layer of fibrous tissue (Fig. 5), in which, rarely, flat, elongated nuclei suggestive of endothedial cells or fibrocytes are noted on the inner surface (Fig. 6). No significant changes were noted in this pseudointima in any of the dogs sacrificed with the Dacron sleeve functioning from 3 to 12 months following implantation (Fig. 7). Fibrous organization of the fibrin appeared first near the ends of the grafts. In all animals, the Dacron sleeve peeled

easily from the surrounding tissue and there was neither gross nor microscopic evidence of growth of fibrous or vascular tissue into the cloth (Figs. 8 and 9). Instead, a thin layer of hyalinized fibrous tissue was apposed to the outer surface of the Dacron, similar in appearance to the material on the inner surface. Rarely, a strand of fibrin lay between the fibers of the cloth. A

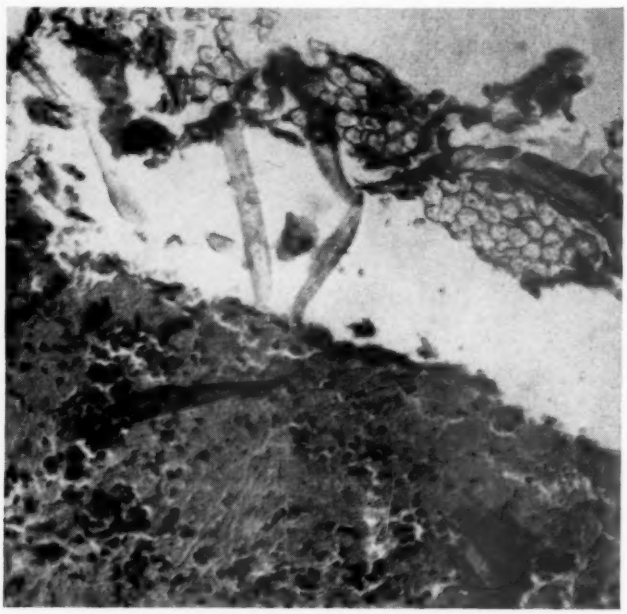


Fig. 3.—Patient L. K., Dacron sleeve removed 12 months after installation. There is no growth of tissue into the cloth. Because of this, it is difficult to hold the Dacron in the sections, which accounts for the ragged appearance in this photomicrograph (H and E, original magnification 125 diameters).

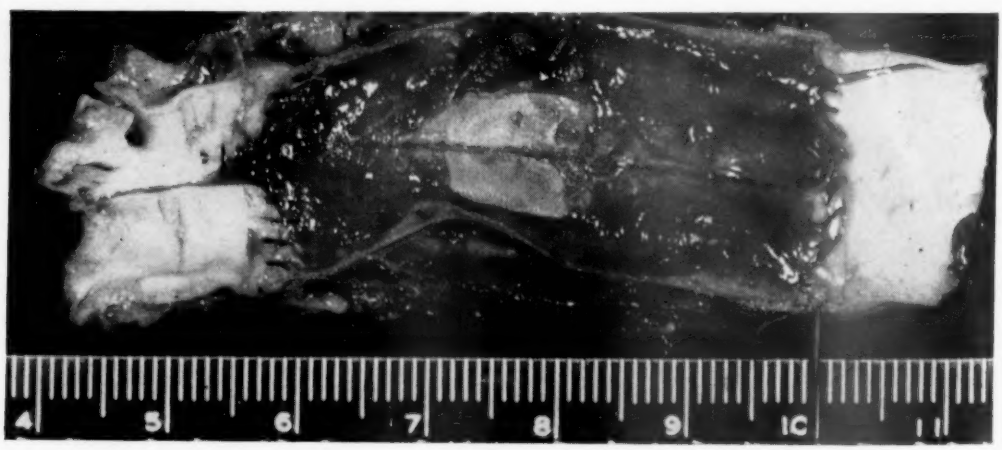


Fig. 4.—Dog 79, 10 days post graft. A thin, glossy layer of fibrin covers the inner surface of the Dacron; this has been peeled away in the center to show the cloth. Note that the cloth separates easily from the surrounding tissue.

mild inflammatory reaction was present in the adjacent adipose tissue. This was most evident in the area where silk suture material had been used to close the Dacron sleeve, and in this area only was there any fixation of graft to surrounding tissue.

DISCUSSION

Dacron sleeve arterial grafts in dogs and in one human functioned as efficient arterial conduits for periods up to 12 months. During this time, the texture and tensile strength of the material remained unchanged. In both human and animal material, a smooth inner surface was formed by material

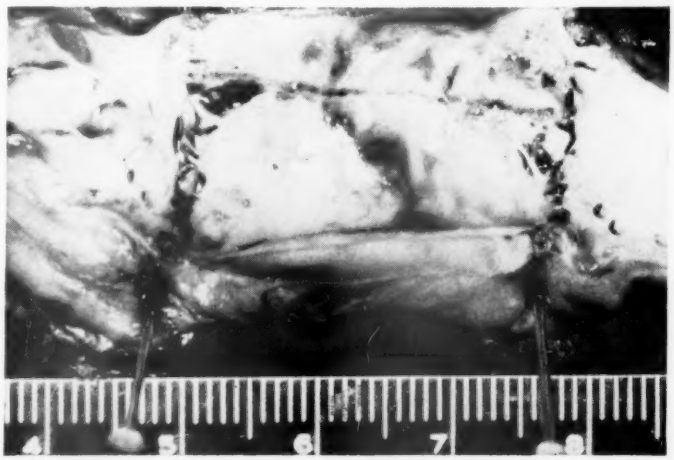


Fig. 5.—Dog 3, 2 months post graft. The inner surface is now opaque, gray-white, and composed of a thin layer of fibrous tissue. The cloth still separates easily from adjacent tissue.

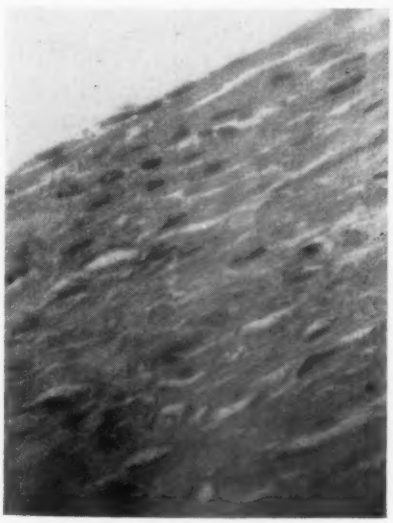


Fig. 6.

Fig. 7.

Fig. 6.—Dog 3, 2 months post graft. A layer of fibrous tissue is seen on the inner surface of the cloth. The flattened cells on the surface are probably fibroblasts (H and E, original magnification 500 diameters).

Fig. 7.—Dog 22, 6 months post graft. Note easy separation of the cloth from the surrounding tissues. The fibrous lining grossly is no different from that seen at 2 months.

which appeared to be hyalinized fibrous tissue. No vascularization of the interstices of the fabric occurred, and a similar layer of fibrous tissue coated the inner surface of the tissue adjacent to the graft. No adherence of the graft

to surrounding tissue was noted. These observations strongly suggest that the pores of the fabric were in no way concerned with the formation or maintenance of the inner lining of the graft.

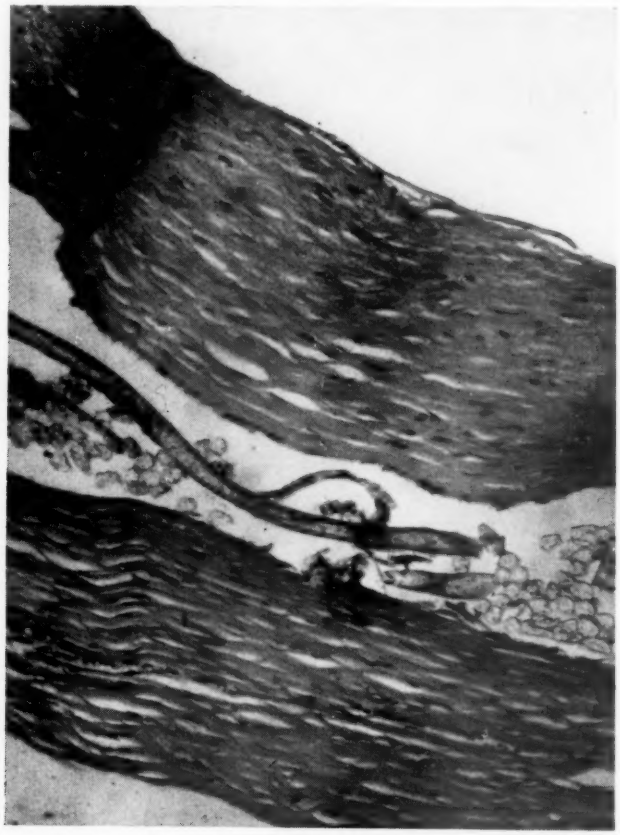


Fig. 8.—Dog 19, 8 months post graft. There is dense fibrous tissue on the inner surface of the graft and apposed to its outer surface. Dacron fibers are seen between the two layers. There is no penetration of the cloth by tissue elements and, therefore, it is difficult to hold the cloth material in the sections (H and E, original magnification 125 diameters).

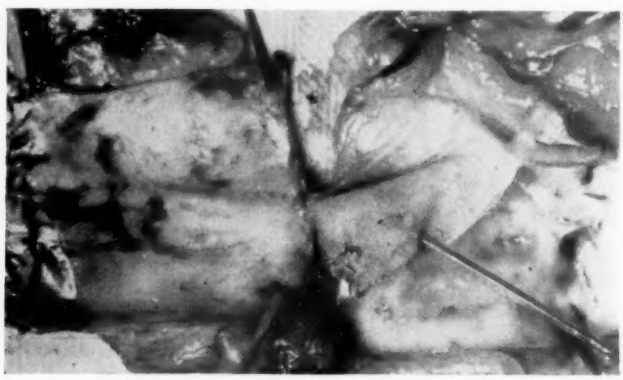


Fig. 9.—Dog 17, 10 months post graft. The opaque, smooth, fibrous lining is similar to that seen at 2 months. The cloth separates easily from the adjacent tissues.

In previously reported experiments, the pores of nylon have been sealed with polythene sheeting[6] and liquid vinyl plastic[7] to make them impermeable. Such material has functioned well when used as an arterial graft and a thin layer of fibrin, which undergoes hyalinization, has formed an inner lining.

This experimental work and our own experience indicate that the porosity of cloth prostheses may not be essential to the development of an intima-like lining or the efficient functioning of a cloth prosthesis as a vascular channel, particularly when grafts of any significant length are employed. Our findings are in accordance with the suggestion of McCune and Blades[4, 5] that the nutrition of tissue lining grafts is predominantly dependent on the blood passing through the lumen.

The lining material has the characteristics of hyalinized fibrous tissue. Endothelial cells could not be identified with any certainty and, therefore, one wonders whether or not endothelium is necessary in the prevention of intravascular clotting.

The final failure of the Dacron graft in the case reported above may have been related to the development of infection. It would not appear that the material used contributed to the failure.

SUMMARY AND CONCLUSIONS

1. The importance of porosity in material used for arterial prostheses is discussed.

2. In all cases, the Dacron employed separated readily from the adjacent tissue, and there was no evidence of growth of either vascular or fibrous tissue into the fabric.

3. In no case did the success of the graft or the maintenance of a smooth intima-like surface seem to depend on the porosity of the material used as a prosthesis.

4. The assumption that cloth arterial replacements serve only as a strut for infiltration and ingrowth by the host's tissue is probably incorrect but will have to await further observation.

REFERENCES

1. Creech, O., Jr., Deterling, R. A., Edwards, S., Julian, O., Linton, R., and Schumacher, H.: Vascular Prostheses: Report of the Committee for the Study of Vascular Prostheses of the Society of Vascular Surgery, SURGERY **41**: 62, 1957.
2. Deterling, R. A., and Bhonslay, S. B.: An Appraisal of Woven Synthetic Prostheses in the Vascular System, A. M. A. Arch. Surg. **72**: 76, 1956.
3. Knox, G., and West, J. P.: Dacron Grafts in the Treatment of Arteriosclerotic Occlusion of the Superficial Femoral Artery, Ann. Surg. **145**: 59, 1957.
4. McCune, W. S., and Blades, B.: The Viability of Long Blood Vessel Grafts, Ann. Surg. **134**: 769, 1951.
5. McCune, W. S., Thistlewaite, J. R., Keshishan, J. M., and Blades, B.: The Nutrition of Blood Vessel Grafts, Surg., Gynec. & Obst. **94**: 311, 1952.
6. Schumacher, H. B., Jr., Harris, E. J., and Sidery, H.: Pliable Plastic Tubes as Aortic Substitutes, SURGERY **37**: 165, 1955.
7. Self, M., Cooley, D., DeBakey, M., and Creech, O.: The Use of Braided Nylon Tubes for Aortic Replacement, Ann. Surg. **142**: 836, 1955.

TRANSPLANTATION OF THE LARGE VENOUS SYSTEM WITH VARIOUS BLOOD VESSEL SUBSTITUTES

An Experimental Study

Itaru Ohara, M.D., D.M.S., and Takeshi Sakai, M.D., Sendai, Japan

(From the Katsura Surgical Clinic, Tohoku University, Faculty of Medicine)

INTRODUCTION

MOST of the operations on the veins have been limited to the peripheral system. Usually, these veins can be permanently ligated without serious postoperative sequelae. Occasionally, the abdominal inferior vena cava below the renal veins has been ligated for bleeding during operation or to prevent the progress of the distal thrombophlebitis.[3, 11] However, interruption of the blood flow through the great veins in the abdomen and thorax is not always without complications. It is well known that obstruction of the superior vena cava is accompanied by edema, engorgement of veins with blood in the upper extremities, and dyspnea.[13] In order to relieve the patient of this syndrome, attempts to resect and replace the lesion with grafts have been successful on several occasions.[1, 5] Blum and co-workers[2] successfully replaced a stenotic abdominal inferior vena cava with a homologous artery. Symptoms were absent for 13 months.

On the other hand, radical operations for malignant tumors are increasing. Although the veins can usually be removed with the tumor as was done by Cope and Hunt[4] for a case of leiomyosarcoma of the inferior vena cava, primary resection of the superior vena cava, inferior vena cava above the renal veins, and the portal vein is usually fatal. In order to facilitate and fulfill the object of the operation, a supply of suitable grafts may be desirable. Several grafts have been tested and the results are reported here.

EXPERIMENTAL PROCEDURE

Method.—Twenty-nine adult mongrel dogs weighing from 6 to 14 Kg. were used. Grafts were placed in the superior vena cava, the thoracic inferior vena cava, and the abdominal inferior vena cava. The operation was performed under endotracheal anesthesia. In cases in which the superior vena cava was used, the chest was entered through the right third intercostal space. Half of the azygos vein was preserved or cut. One to two centimeters of the superior vena cava was resected and replaced with a graft. When the thoracic inferior vena cava was used, the chest was opened through the right seventh

Received for publication Feb. 27, 1957.

Read in part at the Seventh and Ninth General Meetings of the Japanese Society for Thoracic Surgery, Tokyo, Japan, October, 1954 and 1956, respectively.

This study was aided by a grant from the Scientific Research Fund of the Education Ministry for the periods of 1954 and 1956, respectively.

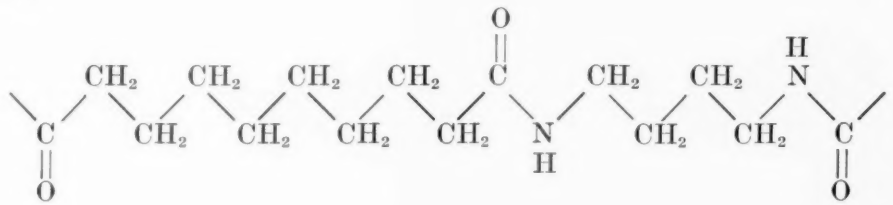
intercostal space and transplantation was carried out between the diaphragm and the right atrium. Most operations were performed under mild hypothermia by the immersion method at an average rectal temperature of 31° C. Transplantation of grafts in the abdominal inferior vena cava was performed below the renal branches.

In general, after the veins were resected 1 to 2 cm., continuous over-and-over and/or interrupted sutures were used for anastomosis. Penicillin, 200,000 units, was administered at the close of the operation. In any case, no antibiotics, blood replacement, or anticoagulants were used postoperatively. The patency of grafts was pursued by venography. Autopsies were performed and histologic studies were made with hematoxylin, eosin, and Van Gieson's stains.

Material.—Three kinds of grafts were used.

1. Alcohol-preserved grafts: The thoracic aortas of dogs or pigs which had been dead less than 24 hours were removed septically and kept in 70 per cent alcohol from 1 to 26 months. When needed, they were removed from the storage bottle aseptically and transferred to physiologic saline solution.

2. Amylan:* Amylan is a polyamine resin with the following chemical formula:



The fiber count is 40 by 38 per square centimeter. The chemical and physical nature is almost the same as nylon.[10] Two forms of fabric were used, taffeta and braided. The latter was a seamless tube, while the former was fashioned by hand into a tube with a seam and cuffs on both ends. Prior to operation these tubes were sterilized by boiling for 5 minutes, with no noticeable changes in their composition.

3. *Silicone rubber tubes†:* The diameter of the silicone rubber tubes (TS 960) used varied from 1 to 2 cm.; their walls were 2 mm. thick and were not transparent. Silicone rubber is brown, compressible, nonwettable, stable to heat, and does not degenerate rapidly. Boiling for 5 minutes is adequate for sterilization.

RESULTS

Twenty-nine grafts, 13 alcohol-preserved homo- or heterologous aortas, 8 Amylan tubes (2 taffeta with a seam and 6 braided without a seam), and 8 silicone rubber tubes, were placed in the venae cavae of 29 adult mongrel dogs.

*Available from the Toyo Rayon Co., 3-5 Nakanoshima, Kitaku, Osaka, Japan.
†Available from the Shibaura Denski Co., Horikawacho, Kawasaki, Kanagawa, Japan.

The Relationship of Patency to Various Substitutes.—

Group 1 (70 per cent alcohol-preserved grafts): Twelve of 13 grafts were transplanted into the superior vena cava; one was transplanted into the abdominal inferior vena cava. The grafts were observed from 6 hours to 6 months. Four grafts were free of thrombus and stenosis 5 days postoperatively. Two showed slight stenosis by the tenth day and severe stenosis

Fig. 1.—Venogram of the superior vena cava with ligated azygos vein in a dog, in which a 70 per cent alcohol-preserved graft was transplanted (indicated by arrows). The graft became obstructed 34 days later. Collaterals are well defined.

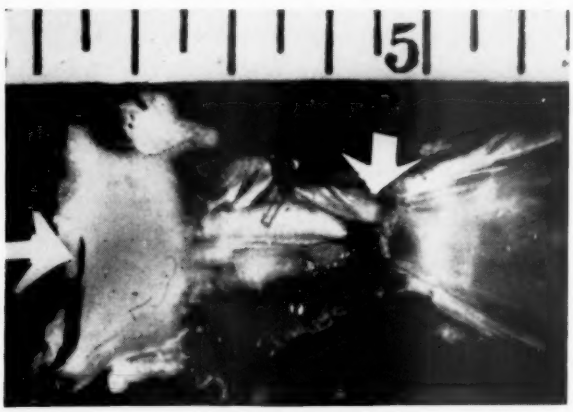


Fig. 2.—A 70 per cent alcohol-preserved graft in the superior vena cava of a dog after 37 days. Severe contraction barely admitted a 2-mm. probe at the proximal anastomosis (right arrow).

by the thirty-seventh day. Six were found completely obstructed in dogs sacrificed 30 days after transplantation. The one abdominal graft was found obstructed 6 months postoperatively. Obstruction of grafts did not disturb the activities of the dogs. Serial venography showed good circulation and

the site of transplantation was hardly visible for the first 5 days. However, the grafts became slightly stenosed on the atrial side after the tenth day, severely stenosed around the thirtieth day, and were usually found obstructed thereafter, with abundant development of collateral circulation around the graft. When stenosis occurred in the superior vena cava, the venous blood of the upper part of the body returned to the heart via the azygos vein. In cases in which the azygos vein had been cut, venous blood circulated through the newly formed collateral system around the obstruction, or the thoracic inferior vena cava, via the internal mammary vein or diaphragmatic vein. At autopsy, the veins in the chest wall were dilated (Fig. 1). Pleural exudate was found in the right thorax in 3 dogs that had survived over 30 days. The anastomosis had immediately become covered with a thin blood layer which

Fig. 3.—Venogram of the abdominal inferior vena cava with Amylan tube (arrows) after 60 days. Complete stenosis of graft with numerous collaterals is visible.

changed to a glistening membrane after 5 to 10 days. Slight stenosis was noticed in a specimen removed on the tenth day, which progressed till the graft completely became obstructed around the thirtieth day (Fig. 2). The stenosis was always found on the atrial side. Microscopically, the gap of anastomosis was immediately filled with a small thrombus which was replaced with fibrocytes by the second week. A month after transplantation, a new epithelium grew over the graft from both ends.

Group 2 (Amylan grafts): Of 8 grafts, 2 were placed in the thoracic inferior vena cava and 6 in the abdominal inferior vena cava. Soon after the clamps were removed following transplantation of the graft, bleeding occurred profusely through the interstices but could be controlled by compression with

a piece of sponge after 3 to 5 minutes. The graft was patent in those 5 which died within 52 hours of transplantation. Of the remaining 3 obstructed grafts, one was patent on the tenth postoperative day as shown by venography but was obstructed on the fortieth day, and the other 2 were found to be obstructed on the fiftieth and sixtieth postoperative day, respectively, at necropsy. Five deaths were attributed to excessive blood loss, of which 2 (dogs with grafts in the thorax) may be accounted for by a long period of circulatory interruption. The other 3 died after venography with injections of sodium iodide. Macroscopically, the inner surface of a graft in a dog which died within 52 hours was covered with a fibrinous membrane. When grafts became obstructed, numerous new collaterals were found around them. These grafts were completely buried in fibrous tissue. When the grafts were opened, the inner surface was wrinkled, forming longitudinal folds and filled with partly organized thrombi. Both anastomoses were stenotic. Venography revealed numerous collaterals running parallel to the collapsed graft (Fig. 3).

Fig. 4.

Fig. 5.

Fig. 4.—The diaphragmatic view of silicone rubber tube grafted in the thoracic inferior vena cava of a dog for 24 days. Severe stenosis occurred on the atrial side, while the diaphragmatic side contracted to 30 per cent.

Fig. 5.—Inner surface of silicone rubber tube which was grafted in the thoracic inferior vena cava of the same dog in Fig. 4. A thin membrane of thrombus 1 mm. thick which could be easily peeled off lined the inside. Left is the atrial side.

Group 3 (silicone rubber tubes): Of 8 grafts, 2 were placed in the abdominal inferior vena cava and 6 in the thoracic inferior vena cava. They were observed from 18 hours to 36 days. All cases but one were operated upon under hypothermia. Patency was observed in 3 grafts. The remaining 5, which were in the body longer than 26 days, showed complete obstruction regardless of their graft site. Abdominal ascites was always found accumulated in those with either stenosed or obstructed grafts in the thorax 15 to 20 days postoperatively. Three of the grafts which were removed 26 days after transplantation were found completely obstructed on the atrial side, whereas the diaphragmatic side was narrowed to 20 to 30 per cent of its lumen (Fig. 4). The internal surface was covered with a smooth layer of thin blood 1 to 2 mm. thick, which could be easily peeled off. This membrane became thicker

with the progress of stenosis and eventually decreased the inside diameter of the graft (Fig. 5). Severe fibrous reaction occurred around the graft, but the graft itself could be detached from it with ease. Return of venous blood was studied by venography and autopsy. With stenosis of the graft, blood found its passage through the azygos vein via lumbar and paravertebral veins, on one hand, while veins of the abdomen and chest wall and intercostal and mammary veins played the other important role.

The Relationship of Patency to the Site of Transplantation.—Of 12 grafts transplanted into the superior vena cava, 6 were patent, while the other half were obstructed. Of 8 grafts transplanted into the thoracic inferior vena cava, 5 were patent, 3 obstructed. Of 9 in the abdominal inferior vena cava, 3 were patent, 6 obstructed. The patent ones had not usually been transplanted over 20 days. Pleural exudate was found in 3 of 12 in the group with superior vena caval grafts, while ascites was found in 4 of 8 in the group with thoracic inferior vena caval grafts. In both groups, the grafts were either severely stenosed or obstructed. None of those in the abdominal inferior vena cava showed ascites.

The Relationship of Stenosis to Suture Methods.—All grafts placed in the superior vena cava and abdominal inferior vena cava were sutured with continuous over-and-over stitches except one distal anastomosis. Interrupted stitches were used in 3 out of 8 grafts in the thoracic inferior vena cava, while the remaining 5 were anastomosed with a combination of continuous and interrupted stitches. Sooner or later, all grafts became obstructed regardless of the suture method.

DISCUSSION

Experimental studies to replace the superior vena cava have been reported by several investigators. Ashburn and associates[1] transplanted freeze-dried arterial homografts in 6 dogs. All showed stenosis at the proximal anastomosis. However, partial success was obtained for 7 months in a case in which an obstruction caused by bronchial carcinoma was relieved by a transplanted freeze-dried pig aorta. Deterling and Bhonslay[5] reported their experiences with aortic homografts, autologous jugular vein, Ivalon, woven nylon, and Dacron. Of 20 grafts in dogs, all except one nylon graft lost their function in a short period of time. More successful were the 4 aortic grafts. Even these showed a 40 per cent reduction of the lumen within several weeks, and furrows and wrinkles after several months. According to their review of 9 clinical cases of patients who had graft replacements in the superior vena cava, 5 femoral autologous veins, 1 homologous graft of vena cava, and 3 aortic homografts were used to relieve inflammatory obstructions. The longest patency was observed in their personal case of a patient with an aortic homograft for 18 months. Egdahl and Hume[6] transplanted polyethylene prostheses lined with venous homografts into 5 superior venae cavae with unsatisfactory results. Our experience with alcohol-preserved grafts was also discouraging. The azygos flow had no influence upon the stenosis. Sauvage and Wesolowski[12] transplanted Orlon cloth into the thoracic inferior venae cavae of growing pigs

and found that they became severely contracted or totally obstructed. We transplanted silicone rubber tubes into the same site in dogs. These grafts showed the same tendency to contract and produce ascites. Originally, silicone rubber seemed to have more elasticity and strength to maintain its form than the other two materials. The silicone rubber grafts became obstructed after about a month. Reaction around the graft caused as much fibrocyte growth as the other two materials. Since grafts in the abdominal inferior vena cava and those in the thoracic vena cava did not function more than approximately 34 days, the site of transplantation may not have any significant effect upon the patency of materials.

It is interesting to note that the graft in the thorax started to contract from the proximal anastomosis. Undoubtedly, the cardiac action and the negative pressure together with fibrous reaction around the graft may be accelerating the collapse of the tube. Neither continuous nor interrupted stitches nor a combination of the two changed the over-all picture of the final results.

Circulation in the superior vena cava with the azygos vein cut may be interrupted for 2 hours,[8] and the abdominal inferior vena cava below the renal veins may be interrupted indefinitely, whereas prolonged interruption of the thoracic inferior vena cava is accompanied by high mortality.[7] According to our study,[9] it may only be safe to interrupt the latter portion for 25 to 30 minutes under normo- or hypothermia.

SUMMARY AND CONCLUSIONS

Seventy per cent alcohol-preserved aortic homografts or heterografts (pig), Amylan (taffeta and braided), and silicone rubber tubes were transplanted into the venae cavae in 29 dogs. Of 13 alcohol-preserved grafts, 12 in the superior vena cava were half patent, while one in the abdominal inferior vena cava was found to be thrombosed 6 months posttransplantation. Of 8 Amylan tubes, 6 braided ones in the abdominal inferior vena cava were half patent, while 2 taffeta ones which were grafted into the thoracic inferior vena cava remained patent for 6 and 36 hours, respectively. Of 8 silicone rubber tubes, 6 in the thoracic inferior vena cava were half patent, while two in the abdomen were found thrombosed 34 and 36 days postoperatively, respectively.

In general, grafts in the vena cava were patent for 5 days and became slightly stenosed after the tenth day. The stenosing process continued to narrow the lumen. Total obstruction of the superior vena cava caused pleural exudate, while obstruction of the thoracic inferior vena cava caused abdominal ascites. When stenosis occurred, venous circulation was taken over by newly developed collaterals around the obstruction, but was only sufficient in the abdominal transplants to prevent complications.

Neither continuous nor interrupted sutures nor a combination of the two prevented stenosis of the graft.

Assistance during operation by Drs. T. Horiuchi, K. Takahashi and T. Yoshida is gratefully acknowledged.

REFERENCES

1. Ashburn, E. S., Sewell, W. H., and Huggins, C. E.: Experimental Replacement of the Superior Vena Cava With Homologous Arteries, and Report of a Case With Malignant Obstruction Replaced With a Heterologous Artery, J. Thoracic Surg. **31**: 618, 1956.
2. Blum, L., Medl, W. T., and Keefer, E. B. C.: Aortic Homograft Substitution for the Postrenal Inferior Vena Cava, A. M. A. Arch. Surg. **72**: 567, 1956.
3. Borton, R., and Lloyd, R. P.: Ligation of the Inferior Vena Cava After Nephrectomy, A. M. A. Arch. Surg. **72**: 194, 1956.
4. Cope, J. S., and Hunt, C. J.: Leiomyosarcoma of Inferior Vena Cava, A. M. A. Arch. Surg. **68**: 752, 1954.
5. Deterling, R. A., Jr., and Bhonslay, S. B.: Use of Vessel Grafts and Plastic Prostheses for Relief of Superior Vena Caval Obstruction, SURGERY **38**: 1008, 1955.
6. Egdahl, R. H., and Hume, D. M.: Nonsuture Blood Vessel Anastomosis. An Experimental Study Using Polyethylene as the Prosthetic Material, A. M. A. Arch. Surg. **72**: 232, 1956.
7. Gerbode, F., and Hultgren, H.: Observations on Experimental Atriovenous Anastomoses With Particular Reference to Congenital Anomalies of the Venous Return to the Heart, and Cyanosis, SURGERY **28**: 235, 1950.
8. Ohara, I., Horiuchi, H., Takahashi, K., Ninomiya, M., Abe, K., and Kikuchi, S.: Ligation and Transplantation of Grafts of the Superior Vena Cava. An Experimental Study, J. Jap. Thoracic Surg. **8**: 433, 1955.
9. Ohara, I., and Sakai, T.: An Experimental Study on Cardiovascular Responses During Interruption of the Inferior Vena Cava in the Thoracic Cavity Under Normo- and Hypothermia, J. Jap. Respiration & Circulation **5**: 295, 1957.
10. Ohara, I., Takahashi, T., Abo, S., and Okamura, H.: Transplantation of the Thoracic Aorta With Amylan Tubes. An Experimental Study, J. Jap. Thoracic Surg. **9**: 369, 1956.
11. Owens, F. M.: Vena Cava Ligation in Thromboembolic Diseases, A. M. A. Arch. Surg. **65**: 600, 1952.
12. Sauvage, L. R., and Wesolowski, S. A.: The Healing and Fate of Arterial Grafts, SURGERY **38**: 1090, 1955.
13. Schlester, M. M.: The Superior Vena Cava Syndrome, Am. J. Med. Sc. **227**: 46, 1954.

ANTIFIBRILLARY DRUGS FOR DEEP HYPOTHERMIA IN THE DOG

PHILIP A. RILEY, JR., CAPTAIN, MC, USAR, BASEL M. MIXON, JR., MAJOR, MC, USA, AND TIMOTHY G. BARILA, MAJOR, MC, USA, WASHINGTON, D. C.

(From the Department of Experimental Surgery, Walter Reed Army Institute of Research, Walter Reed Army Medical Center)

INTRODUCTION

SEVERAL drugs have been reported to have an antifibrillatory effect on the hearts of dogs undergoing experiments on immersion hypothermia for intracardiac surgery at temperatures around 25° C. Some of these drugs are Prostigmin,[3] Arfonad,[5] and chlorpromazine. Sympathectomy has also been used as a protective measure under the same circumstances.[5]

At present, two of the limiting factors in the clinical use of hypothermia are the occurrence of ventricular fibrillation and the limited time available for surgery with the heart excluded from the circulation. If lower temperatures are to be used to prolong the operating time, ventricular fibrillation must be prevented. The above drugs and sympathectomy were studied in dogs to determine whether lower temperatures could be reached without the occurrence of ventricular fibrillation. The effects of these measures on resuscitation and survival were also noted.

METHOD

Adult healthy mongrel dogs weighing between 9.6 and 20.4 Kg. were anesthetized with either thiopental (2½ per cent) or pentobarbital (6 per cent) intravenously and clipped. An endotracheal tube was inserted and connected to an automatic respirator utilizing room air. The rate and volume of the respirator were adjusted to produce moderate hyperventilation. A cannula was inserted through the femoral artery into the aorta and connected to a Statham strain gauge. Another cannula was inserted through the femoral vein into the inferior vena cava when additional drugs were to be given. A continuous standard limb lead electrocardiogram and blood pressure tracing were recorded by a Sanborn Polyviso throughout the experiment. One thermocouple was inserted 10 cm. into the rectum and another thermocouple into the esophagus 18 cm. from the incisor teeth. Continuous temperature recordings were made by a Brown potentiometer. Esophageal and rectal temperatures were usually within a degree of each other, above 20° C. Cooling below 20° C. reduced the rectal temperature more rapidly than the esophageal temperature. The reverse was true during rewarming; the rectal temperature rose faster than the esophageal temperature until they became parallel at 18 to 20° C. and remained so throughout the warming period. Henceforth, all references will be to the rectal temperature.

The animal was immersed in an ice bath at 4° C., excluding the head. Shivering was controlled throughout the cooling phase by the additional injection of either sodium thiopental or sodium pentobarbital. The animals were

Received for publication Feb. 28, 1957.

cooled until ventricular fibrillation occurred or until the animal's temperature reached 17° C. At the onset of ventricular fibrillation the respirator was disconnected and the ice water drained. After allowing ventricular fibrillation to continue for 30 minutes, resuscitation was begun. Resuscitation consisted of performing a left thoracotomy and manual massage of the heart during continuous warm saline irrigation of the thoracic cavity. A 150-volt, 0.1 second electric shock was applied to the heart at every degree centigrade rise in rectal temperature until defibrillation occurred. After the animal's temperature reached 28° C., the result was considered a failure. No resuscitation drugs were used.

The animals which did not exhibit ventricular fibrillation were cooled to 17° C., at which time the ice-water bath was slowly warmed to a maximum of 45° C. The animal's temperature usually continued to skid another 1 to 2° C., giving a minimal temperature in the majority of the nonfibrillating dogs in the range of 15 to 16° C. The end point of 17° C. was selected because all but 3 of a previous group of 42 dogs developed ventricular fibrillation in this range.[4] All animals were rewarmed in the water bath to 35° C. and returned to their cages. Neurologic damage in the survivors was estimated grossly by the animal's orientation and his ability to see, eat, stand, walk, and run.

A total of 119 animals were divided into 12 groups according to the drugs used. The amounts of additional drug given are shown in Table I.

TABLE I. TOTAL AMOUNT OF DRUG (MILLIGRAMS PER KILOGRAM) GIVEN DURING HYPOTHERMIA EXPERIMENT

	PENTOBARBITAL				THIOPENTAL			
	CHLORPROMAZINE	CONTINUOUS ARFONAD	ARFONAD AT 23° C.	PROSTIGMIN	CHLORPROMAZINE	CONTINUOUS ARFONAD	ARFONAD AT 23° C.	PROSTIGMIN
Minimum	0.5	0.03	0.02	0.08	4.9	0.03	0.008	0.06
Maximum	5.2	11.5	0.13	0.27	20.5	0.84	0.08	0.03
Average	2.2	2.2	0.05	0.13	9.9	0.30	0.03	0.15

Pentobarbital.—The first 6 groups had sodium pentobarbital (25 mg. per kilogram) as the basic anesthetizing agent.

Group I. Controls: Twelve dogs were used as controls and were given the induction dose of 25 mg. per kilogram pentobarbital. This was usually sufficient to control shivering throughout cooling, but if shivering occurred 60 mg. supplementary doses of pentobarbital were given.

Group II. Pentobarbital with chlorpromazine: Nine dogs received chlorpromazine in divided doses throughout cooling.

Group III. Pentobarbital with continuous Arfonad: Eight dogs were anesthetized with pentobarbital. Before cooling was initiated, a continuous intravenous drip of Arfonad (0.05 mg. per cubic centimeter) was started to maintain the blood pressure in the range of 75/40 mm. Hg. The precooling rate of drip was continued throughout cooling until ventricular fibrillation occurred, at which time the drug was discontinued.

Group IV. Pentobarbital with Arfonad at 23° C.: Eight dogs were anesthetized with pentobarbital and when their rectal temperatures reached 23° C., they were given intravenous Arfonad (0.1 mg. per cubic centimeter) sufficient to lower the systolic blood pressure to 50 mm. Hg. This was given over a 2-minute period. This temperature was selected because it was high enough above the average temperature of ventricular fibrillation in the control group (20.7° C.) to give the drug time to act and yet low enough not to be completely metabolized before ventricular fibrillation normally would occur.

Group V. Pentobarbital with Prostigmin: Seventeen dogs were anesthetized with pentobarbital and given intravenous Prostigmin (1 mg. per cubic centimeter) when their rectal temperature reached 23° C. The Prostigmin was given in a quantity sufficient to lower the heart rate to approximately 6 to 12 times per minute (Table I). This dose also caused a lowering of the blood pressure, constriction of the pupils, and defecation.

Group VI. Pentobarbital with sympathectomy: Two dogs had a 2-stage bilateral dorsal transthoracic sympathectomy from T_1 through T_7 and including the dorsal (stellate) ganglion. The dogs were allowed to recuperate for 10 days after the second stage before being used in the hypothermia experiments. They were anesthetized with pentobarbital for the cooling.

Thiopental.—The second 6 groups had thiopental (30 mg. per kilogram) for induction of anesthesia. This dose was sufficient to prepare the animal for the experiment and to begin the cooling. Additional increments of 100 mg. of thiopental were given to control shivering throughout cooling. Shivering seldom occurred below 27° C.

Group VII. Thiopental controls: Nineteen dogs constituted this group, receiving only thiopental throughout cooling.

Group VIII. Thiopental with chlorpromazine: Nine dogs were anesthetized with thiopental and given chlorpromazine throughout cooling. In initial experiments, chlorpromazine was given to control shivering. When it became obvious that the drug did not abolish shivering, thiopental was given to control shivering and the chlorpromazine was administered in divided doses during cooling.

Group IX. Thiopental with continuous Arfonad: Twelve dogs were anesthetized with thiopental and started on a continuous intravenous Arfonad (0.05 mg. per cubic centimeter) drip prior to cooling, as in Group III. Shivering was controlled with additional thiopental.

Group X. Thiopental with Arfonad at 23° C.: Eight dogs were anesthetized throughout cooling with thiopental and received Arfonad at 23° C., as in Group IV.

Group XI. Thiopental with Prostigmin: Eleven dogs were anesthetized with thiopental throughout cooling and given Prostigmin at 23° C., as in Group V.

Group XII. Thiopental with sympathectomy: Three dogs had prior sympathectomy, as in Group VI, and were anesthetized with thiopental for the cooling.

RESULTS

Incidence of Ventricular Fibrillation.—The incidence of ventricular fibrillation is illustrated graphically in Fig. 1 for the dogs receiving pentobarbital and in Fig. 2 for the dogs receiving thiopental. The mean low temperature of the same groups is represented in Figs. 3 and 4. This has been calculated by averaging the temperature of ventricular fibrillation in animals who fibrillated and the lowest temperature reached in those who did not fibrillate.

Chlorpromazine offered no protection against ventricular fibrillation in either group, nor did it lower the mean low temperature.

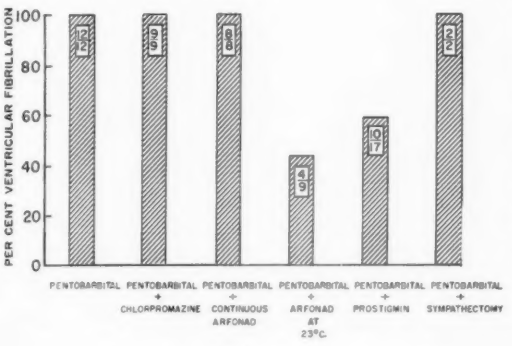


Fig. 1.

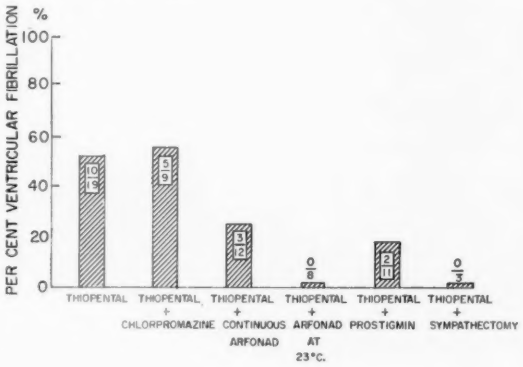


Fig. 2.

Fig. 1.—Incidence of ventricular fibrillation in the pentobarbital groups.
Fig. 2.—Incidence of ventricular fibrillation in the thiopental groups.

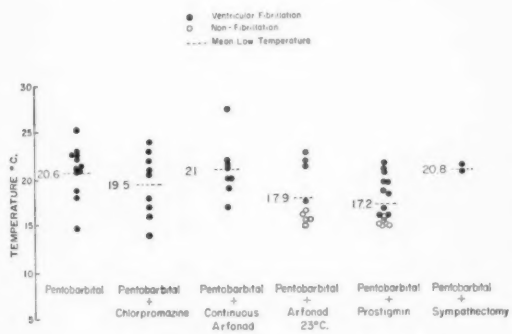


Fig. 3.

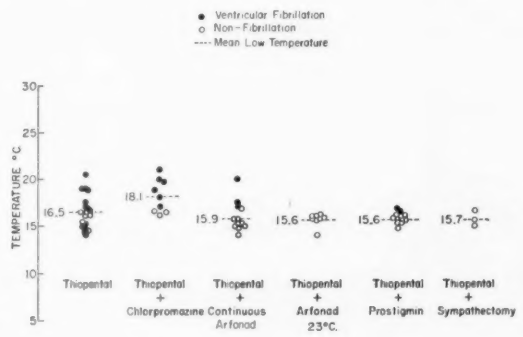


Fig. 4.

Fig. 3.—Scattergram comparing pentobarbital groups.
Fig. 4.—Scattergram comparing thiopental groups.

When Arfonad was given continuously throughout cooling, it did not influence either the incidence of ventricular fibrillation or the temperature at which fibrillation occurred in the pentobarbital group. In the thiopental group, the incidence of fibrillation was reduced. The amount of Arfonad received was far greater in the pentobarbital group than in the thiopental group (Table II). These averages were increased, however, by the amount of Arfonad received by one dog which fibrillated despite 11.5 mg. per kilogram. In the thiopental–continuous Arfonad group, the fibrillators received an average of only half as much Arfonad as the nonfibrillators (Table II).

TABLE II. AVERAGE AMOUNT OF DRUG (MILLIGRAMS PER KILOGRAM) GIVEN DURING HYPOTHERMIA EXPERIMENTS

	PENTOBARBITAL				THIOPENTAL			
	CHLORPROMAZINE	CONTINUOUS ARFONAD	ARFONAD AT 23° C.	PROSTIGMIN	CHLORPROMAZINE	CONTINUOUS ARFONAD	ARFONAD AT 23° C.	PROSTIGMIN.
Survivors	--	0.10	0.03	0.10	11.7	0.36	0.02	0.14
Nonsurvivors	2.2	2.86	0.10	0.14	6.3	0.19	0.03	0.15
Fibrillators	2.2	2.17	0.05	0.15	9.9	0.19	---	0.07
Nonfibrillators	--	---	0.05	0.11	9.9	0.38	0.03	0.17

In both groups given Arfonad at 23° C., the incidence of ventricular fibrillation was reduced. Similarly, the incidence was reduced in both of the groups given Prostigmin. The nonfibrillators in the thiopental–Prostigmin group received an average amount of Prostigmin twice that of the fibrillators. However, in the pentobarbital group, there was little difference (Table II).

Only 2 sympathectomized dogs were given pentobarbital anesthesia and, while both incurred ventricular fibrillation in the expected range, none of the 3 sympathectomized dogs under thiopental anesthesia fibrillated.

SURVIVORS

Only animals which lived longer than 7 days were considered as survivors. Fig. 5 represents the survivors of the groups receiving pentobarbital, and Fig. 6 represents the survivors receiving thiopental.

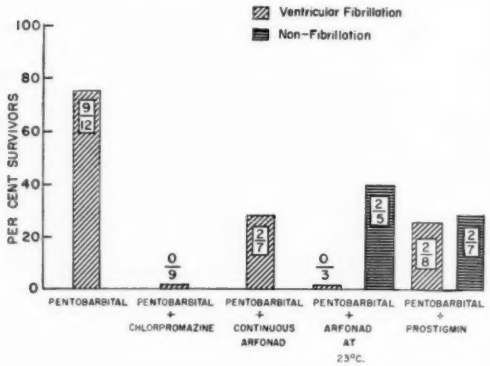


Fig. 5.

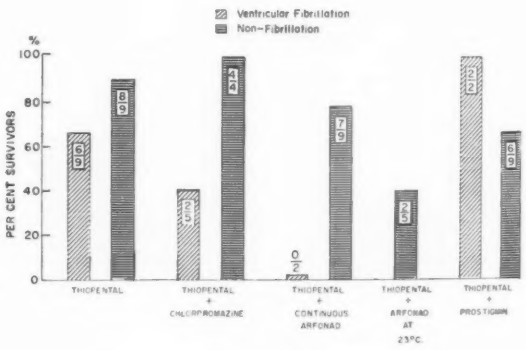


Fig. 6.

Fig. 5.—Incidence of survival in the pentobarbital groups.
Fig. 6.—Incidence of survival in the thiopental groups.

The sympathectomy groups are not represented in the graph, because of the small number. One of the sympathectomized animals with pentobarbital anesthesia which fibrillated was a survivor. The other sympathectomized dog which fibrillated and the 3 receiving thiopental anesthesia which did not incur ventricular fibrillation did not survive.

None of the animals anesthetized with pentobarbital and given chlorpromazine during cooling survived. When thiopental was used as the anesthetic agent, 2 of the 5 animals incurring ventricular fibrillation survived and all of the nonfibrillators survived.

Only two animals survived ventricular fibrillation of 7 attempts at resuscitation in the pentobarbital–continuous Arfonad group. Neither of the 2 attempts at resuscitation following fibrillation with thiopental and continuous Arfonad were successful, while 7 of 9 nonfibrillators with this latter combination of drugs survived.

The incidence of survivors was low in both groups given Arfonad at 23° C. The group receiving pentobarbital had fewer survivors than the group receiving thiopental anesthesia. The average amount of drug received in the surviving animals is quite comparable to the average amount received by the nonfibrillators, as shown in Table II.

Four of the survivors had gross neurologic damage. Three of these were thiopental controls, one of which had developed ventricular fibrillation. The fourth animal was in the pentobarbital with continuous Arfonad series and had fibrillated.

COMMENTS

Thirty-six animals died following attempted resuscitation after ventricular fibrillation. Seven of these deaths (19 per cent) occurred in the postoperative recovery ward while the remaining 29 (81 per cent) never left the operating room. Thus, the majority of animals incurring ventricular fibrillation died as a result of the experiment and not from postoperative complications.

All of the animals were defibrillated by electric shock. The most frequent cause of failure following defibrillation was the animal's inability to develop and maintain a satisfactory blood pressure. Likewise, the tone of the heart during massage was very poor in the majority of the failures. This was especially notable in the chlorpromazine-treated groups. Although epinephrine might have aided the cause of the hearts with poor muscular tone, no additional drugs were used.

DISCUSSION

While pentobarbital is not a drug used in clinical anesthesia, we chose to use it in these experiments because of our previous findings in experiments on ventricular fibrillation in the hypothermic dog.[4] In 42 dogs anesthetized with pentobarbital, ventricular fibrillation occurred in all. Thus, we felt it would be easier to judge the effect of any given antifibrillatory agent if this drug were used for basal anesthesia.

Montgomery, Prevedel, and Swan[3] have demonstrated the protection from ventricular fibrillation during hypothermia for intracardiac surgery afforded by vagal stimulation, acetylcholine, and Prostigmin. They attributed their successful results to the establishment of a more normal balance of sympathetic and parasympathetic effects following a depression of the latter during hypothermia. If this is the case, the cause of fibrillation in our sympathectomized dogs given pentobarbital anesthesia might be due to the parasympatholytic properties of pentobarbital. Similarly, the protection afforded the animals given thiopental might be due to the cardiac vagal enhancing properties which are peculiar to the thiobarbiturates.[1] The addition of adrenergic blocking agents might have further clarified this point.

McCubbin and Page[2] have shown that the principal vasodepressor effect of Arfonad is by direct vasodilatation and that its ganglionic blocking properties are of a secondary nature. The sympatholytic action of Arfonad is likely the reason for its protective action against ventricular fibrillation. This sympatholytic property of Arfonad may have been somewhat neutralized by the parasympatholytic properties of pentobarbital to explain the failure of Arfonad to prevent fibrillation in a larger number in that series.

An important consideration of an antifibrillatory agent is the effect on the heart in the event that ventricular fibrillation should occur. With the exception of 2 dogs fibrillating with thiopental and Prostigmin, all groups given addional drugs had a decreased incidence of survival following ventricular fibrillation when compared to the control series.

There were no survivors in the pentobarbital-chlorpromazine series.

While some of the drugs used in these experiments did decrease the incidence of ventricular fibrillation, the beneficial effect of their use clinically to permit deeper hypothermia for longer operating times with cardiac occlusion is doubtful. Possibly a combination of antifibrillatory drugs would be preferable, if drugs are available to counteract the antifibrillatory drugs, should ventricular fibrillation occur.

SUMMARY

1. A total of 119 immersion hypothermia experiments were done to determine if various antifibrillatory agents would permit cooling dogs to a lower temperature. The effects of the drugs on cardiac resuscitation when ventricular fibrillation did occur were also noted. The drugs tested were chlorpromazine, Arfonad and Prostigmin, combined with pentobarbital or thiopental anesthesia. The effect of sympathectomy was also tested.

2. Arfonad given at 23° C. and Prostigmin combined with either pentobarbital or thiopental decreased the incidence of ventricular fibrillation. Continuous Arfonad throughout cooling with thiopental anesthesia decreased the incidence of fibrillation, but with pentobarbital anesthesia continuous Arfonad did not decrease the incidence of ventricular fibrillation. Chlorpromazine did not affect the incidence of ventricular fibrillation in either group.

3. There was a decreased incidence of survival from ventricular fibrillation following attempted resuscitation in all groups, except that receiving thiopental and Prostigmin, when compared to control groups.

REFERENCES

1. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1955, The Macmillan Company.
2. McCubbin, J. W., and Page, I. H.: Nature of the Hypotensive Action of a Thiophanium Derivative (RO 2-2222) in Dogs, J. Pharmacol. & Exper. Therap. **105**: 437-442, 1952.
3. Montgomery, A. V., Prevedel, A. E., and Swan, H.: Prostigmin Inhibition of Ventricular Fibrillation in the Hypothermic Dog, Circulation **10**: 721-727, 1954.
4. Schafer, P. W., Hughes, C. W., and Barila, T. G.: Tolerance of the Hypothermic Normal Dog's Heart to Ventricular Fibrillation, A. M. A. Arch. Surg. **70**: 723-728, 1955.
5. Shumaker, H. B., Jr., Riberi, A., Boone, R. D., and Kajikuri, H.: Ventricular Fibrillation in the Hypothermic State. IV. The Role of Extrinsic Cardiac Innervation, Ann. Surg. **143**: 223-229, 1956.

A NEW INSTRUMENT FOR PREPARING ARTERIAL HOMOGRAFTS

CLEMENT A. HIEBERT, M.D., AND ROBERT R. LINTON, M.D., BOSTON, MASS.

(From the Department of Surgery, Massachusetts General Hospital)

DURING the past 5 years great strides have been made in the treatment of obliterative arterial disease of the lower extremities secondary to atherosclerosis by the utilization of vascular grafts implanted in the extremity to by-pass occluded areas involving the femoral artery. The most satisfactory graft in our hands has been the human arterial homograft, preserved by the frozen irradiated method described by Meeker and Gross.[2]

One of the drawbacks to the arterial homograft in many clinics is the difficulty of procurement of these blood vessels and the maintenance of a well-stocked blood vessel bank. As a result the search for a satisfactory synthetic plastic vascular prosthesis has been intensified. Although it is the hope that one will be found which will prove as satisfactory as an arterial homograft, none as yet has been developed, especially for the grafting procedures that require long grafts of 50 to 60 cm. in length. Another drawback to arterial homografts is the laborious and time-consuming task of preparing the vessels at the time of the operative procedure, since they cannot be prepared prior to surgery. This consists of the meticulous cleaning of the vessel wall of all excess tissue and the individual ligature of all its tributaries. This ordinarily requires two persons, the surgeon and an assistant, or two assistants to accomplish it satisfactorily.

At first thought it seems logical that this should be done at the autopsy table when the grafts are obtained. This, however, is neither practical nor sound because the vessels are usually obtained by one person who cannot do it mainly from the viewpoint of expediency. It is also important that as little time as possible elapse between the taking of the graft and its quick freezing. Hufnagel[1] also has advised against ligature of the branches prior to the freezing of the graft because of the difference in the coefficient of contraction of the ligature and the blood vessel wall which might result in weakening of the latter at the points of ligature. For these reasons it has been our practice to ligate or suture these branches at the time of the grafting procedure. As a rule, there are 15 to 20 such tributaries which must be secured in a long iliofemoropopliteal graft. It is necessary first to clean the arterial wall of the excess fibrous tissue in order to isolate and ligate the branches. This requires at least two persons, if the graft is held manually, working steadily for an hour. It must be done with great care since not only a limb but a life depends on the thoroughness with which it is performed.

Received for publication Feb. 19, 1957.

An attempt has been made to facilitate the preparation of the homografts by the use of the easily autoclaved blood vessel holder shown in Fig. 1. Trauma to the graft at this time is greatly reduced also and, when short-handed, by means of it the graft can be prepared by one assistant.

The instrument consists of a base with a central bar and a crossbar at each end to stabilize it. A vertical upright is attached to one end of this base. A bulldog clamp to hold one end of the homograft is attached to a rotating shaft that goes through the upper end of the upright. The other upright slides on the central bar to which it can be fixed with a thumb-set screw, thereby allowing the instrument to be adjusted to the length of the graft. In the upper end of this upright, a rotating pagoda-like shaft is attached, the center of which has been drilled to permit the introduction of a heparin solution into the graft through a rubber tube attached to the end of the rotating shaft. The concentric rings of increasing caliber permit easy attachment to it of grafts of varying diameter. The vessel is secured to it by means of a stout ligature. The inset *(A)* gives the dimensions of the pagoda-like rotating shaft.

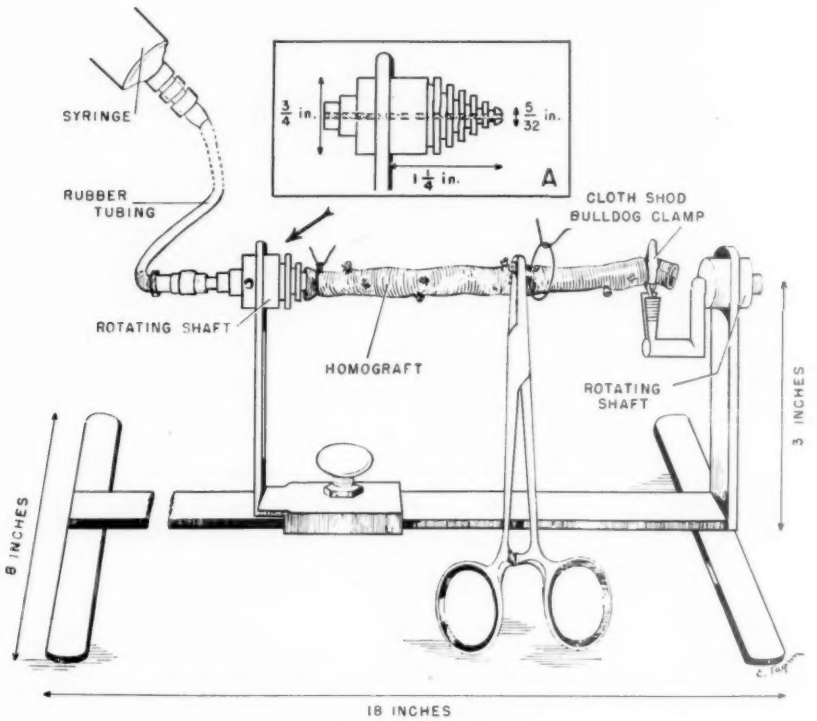


Fig. 1.

In practice, once the length of the graft has been ascertained, an assistant leaves the operating team, selects a suitable vessel from the blood vessel bank, and prepares it, alone if necessary, at a separate sterile table, while the surgery on the patient continues to develop the field for the implantation of the graft. The homograft is thawed by placing it in a 0.01 per cent solution of heparin in

saline solution at room temperature. This requires approximately 5 minutes. Then, it is strung out between the bulldog clamp and the pagoda-like end to which it is secured with a stout ligature. Both ends of the apparatus allow the vessel to be turned as a unit. This permits easy access to its entire circumference so that the tributaries may be exposed and ligated with ease. The graft is first flushed out with the weak heparin solution by introducing it through the rubber tube attached to the pagoda-like end and leaving the vessel unclamped at the other end to make certain there are no blood clots left within the graft lumen. The free end of the homograft is then secured in the bulldog clamp putting the blood vessel on a slight amount of tension. This facilitates the cleaning of the vessel wall and the isolation of the tributaries. The larger of the branches are first ligated, then the graft is distended with heparin solution to facilitate the isolation and the tying of the smaller branches that would otherwise be difficult to find. The stand is constructed so that the handle of a fine hemostat after clamping a branch will rest on the table at an angle to permit easy ligature of it without additional assistance if it is not available.

SUMMARY

A new instrument is demonstrated to facilitate the preparation of arterial homografts. With its use this can be accomplished with a minimal amount of trauma and, in addition, in case of a shortage of operating personnel, one assistant alone can prepare the graft.

REFERENCES

1. Hufnagel, C. A.: Personal communication.
2. Meeker, I. A., Jr., and Gross, R. E.: Sterilization of Frozen Arterial Grafts by High Voltage Cathode-Ray Irradiation, SURGERY 30: 19, 1951.

Editorial

CONDUCTED BY I. S. RAVDIN, M.D.

A Plea for Factual Summaries

Next to the title, the most important section of a medical article is the summary. To the indexer, a properly written summary furnishes the necessary clues for cross-indexing the article. To the busy abstractor, it is a welcome digest of endless pages of printed words. To the assiduous physician, daily flooded with more literature than he can possibly peruse, it is the sample of a product which he must decide whether or not to purchase. But, unfortunately, too many authors fail to take advantage of this opportunity to sell their product by offering their prospective customers a truly representative sample, that is, a concentrated form of the real product.

To write a factual summary of an article requires considerable time and thought. The author's temptation to dismiss its preparation lightly, after he has labored long and hard with the paper itself, is perhaps understandable. By the time he is ready to summarize the article, he is both weary and relieved at having completed the tedious task of preparing the report. Yet he feels compelled to write some kind of ending. To satisfy this compulsion he hastily jots down, "So many cases have been reviewed," or "Such and such an instrument or operation has been described," or "The results have been analyzed," depending on the type of paper he has written. This tells the prospective customer nothing he has not already learned from the title. The reader wants to know the kind and number of cases and reasons for presenting them, a brief description of the method or instrument devised, or the kind of treatment used and the exact results obtained. In other words, he expects to find in the summary specific information in as few words as possible.

Perhaps one solution to the preparation of a satisfactory summary would be to write this section of the paper first while the author is fresh and energetic and the purpose and main points he wishes to make are uppermost in his mind. Then, after he has written the paper, he may review this summary to make certain that it actually is a recapitulation of the article he has prepared. Incidentally, many editors, realizing the value of a sample in selling a product, are now placing the summary in a prominent position on the title page of the article, usually between the title and the introductory paragraph or in a blocked off section of the printed columns.

An informative summary should tell the reader as succinctly as possible the reason the paper was written and the salient points made in it. And it is just as important to know what not to include in the summary as what to

include. For instance, no new facts should be introduced in the summary that have not already appeared in the body of the paper. Furthermore, there is no need to document statements made in the summary by citing references, as this should have been done in the body of the article. And, finally, reference should never be made in the summary to tabular or graphic material, as this also belongs in the body of the paper.

In conclusion, the summary should be a capsule version of the paper. A factual summary is one that will whet the appetite of the reader so that he will go back for a second helping.

—Michael E. DeBakey
Cora and Webb Mading
Department of Surgery
Baylor University
Houston, Texas

Reappraisal

CONDUCTED BY CLARENCE DENNIS, M.D. ASSISTED BY ALFRED HURWITZ, M.D.

USE OF PROTEOLYTIC ENZYMES AS DÉBRIDING AGENTS

EDWARD L. HOWES, M.D., NEW YORK, N. Y.

(From the Department of Surgery, Columbia University)

WHEN, after injury, the body liquefies dead tissue or sets up a line of separation between itself and necrotic tissues, these changes result from activity of proteolytic enzymes. The clotting of the blood and the struggle between the bacteria and the tissues invaded involve enzymatic activities. We should be able to help these naturally occurring enzymes if we understand their characteristics and how they function, and perhaps we can help still more by supplying proteolytic enzymes from external sources. This type of approach to the pathologic physiology of injury is a young developing field. Although considerable study has been made of the use of enzymes to aid surgery in the past 5 years, the results obtained must be regarded as early attempts which will be considerably modified by the acquisition of additional knowledge on the nature and action of these catalysts.

Since "Use of Enzymes in Surgery" was printed in April, 1956,[9] there have been several interesting developments.

The intravenous use of streptokinase-streptodornase (SK-SD) to increase the amount of circulating enzyme, plasmin, has not reached fruition. However, plasmin (fibrinolysin) has been isolated from human blood and has been used clinically.[3, 4] The number of cases treated for intravascular clotting is not yet large enough to evaluate.

On the other hand, the successful local use of SK-SD and plasmin continues to be reported together with use of other proteolytic enzymes, trypsin and papain. But skepticism exists about the therapeutic role of enzymes, especially when they are used to treat self-limited diseases like drained abscesses that heal anyway, and this skepticism mounts further when the enzyme is used locally with the parenteral administration of antibiotics. Indeed, some of the subjectivity present in such observations becomes apparent when "good results" are reported with the local use of enzyme preparations that do not display any evidence of activity whatsoever when tested in the laboratory.

Fortunately, there are simple tests—the gelatine photographic plate method, the azocol tests, and the casein digestion test—that can be used to test for the proteolytic activity of the original preparation and to evaluate its retained efficiency later. With them it is possible to select ointments and pastes

that will allow the enzymes to work, and moreover it has been found that certain preparations will retain activity with proper conditions of storage. Some antibiotics can be added also to a concentration that will not interfere with the activity of the enzyme. In general, we have found that if the enzyme or enzyme preparation is shown to be active in the laboratory, then and only then have we a reasonable chance clinically to eliminate inhibiting factors that make it possible for the enzyme to act against its proper substrate.

Many reasons have been found why the enzyme can fail as therapeutic agents. Enzymes are proteins; consequently some are destroyed by bacteria, some by other enzymes, and some may even destroy themselves. Enzymes and enzyme preparations must have sufficient shelf life to be still potent when applied. They must be used in vehicles from which they can escape, and, lastly, substances should not be added to help them on a theoretic base unless tested first to be certain they do not inhibit activity. For example, the action of most enzymes is stopped by the addition of heavy metals frequently found in antiseptics and sometimes in preservatives. Urea, to illustrate further, that is keratolytic and swells collagen at a 25 per cent concentration, does not have this property at a lower concentration and indeed may interfere with the action of enzymes.

The most potent enzyme or enzyme preparation will not work clinically if it is applied to a lesion possessing chemical or physical circumstances unfavorable for its activity of if the substrate presenting in the lesion has been altered in some way. The necessity of correcting the environment to allow the enzyme to work against its proper unaltered substrate is one of the most difficult concepts to grasp about enzyme therapy. There must be moisture, the pH must be favorable, and there must be contact with the substrate to be digested. The substrate must not be altered by previous treatment with antiseptics or by other chemical or physical states that "leatherize." If the proper environment is achieved and the substrate is not altered, only small amounts of enzymes are required for spectacular results; while if it is not achieved, the quantities of enzyme used will not make any difference.

To evaluate the success of any enzyme therapy, we can only appraise when we can be certain that the causes of failure have been eliminated. The causes of failure are (1) lack of a potent enzyme; (2) use of it against an improper substrate, as for example, use of a proteolytic enzyme against bone or cartilage; (3) use of other chemicals or adjuvants for some other therapeutic purpose that either destroy the enzyme or set up an inhibiting environment; (4) failure to restrain excessive bacterial growth; and (5) conversion of the substrate to an insoluble form that the enzyme cannot attack.

Before we evaluate some of the therapeutic trials made with use of proteolytic enzymes as débriding agents, it should be pointed out that there are no circulating enzymes in the body to digest collagen. Pepsin has the capacity but its activity is limited to the lumen of the stomach. The trypsin-like enzymes will digest collagen if it is denatured, but this process of denaturation in the body is apparently very slow. Collagen is the principal constituent of skin,

fascia, tendon, and connective tissues. When collagen becomes separated from its blood supply, it remains undigested as a mass of "slough," so-called perhaps because it has not sloughed. When burned, collagen of the skin becomes only partially denatured. Most of it remains undenatured. There is then a very good reason why a collagenase from an external source should be used to débride burns. The body also has no enzymes to digest bone or saponified fats. On the other hand, the body has enzymes to lyze fibrin, muscle, fat, nerve tissue, and epithelial cells when they are separated from their blood supply. The blood supply protects these structures by means of antienzymes and other nonspecific substances that increase locally after an injury.

Considering that SK-SD[14] activates plasmin that only digests fibrin, burn slough could not be digested unless SK-SD or plasmin attract more leukocytes to give up enzymes that again would only digest after denaturation. I used pepsin originally as a débriding agent. The acid pH necessary for its activity was difficult to maintain. This trial of pepsin plus acid was quickly supplanted by the application of organic acids only, pyruvic acid and others, of high buffering capacity that acted as denaturants and swelling agents of burned collagen.[6, 8] When these acids were applied to burns, the necessary proteolytic enzymes had to come from the leukocytes again, so that separation of slough could not be started until about the seventh day and moreover penetration of the acid and denaturation of the burn to the depth where the leukocytes accumulated could not be accomplished always. Hence sometimes pyruvic acid worked brilliantly and at other times would not work at all. Trypsin, first used by Siler,[13] attacks only denatured collagen and in addition is an enzyme of short life, is easily destroyed by bacteria, and is often offset by the presence of antitrypsin. The danger envisaged, that protein shock might follow its application to an extensive denuded area, did not materialize. Since crystallization, trypsin has been injected into tissues.

There are other enzymes of vegetable origin with activities similar to trypsin—ficin (bromelin), papain—and many others, called proteinases obtained from molds. Ficin attacks undenatured collagen under certain circumstances, but may cause bleeding. Papain needs an activator; cysteine or sodium salicylate. When the latter was used by Beard[2] it was absorbed and caused a toxicity problem. With cysteine, the attack was still only against denatured collagen and Beard soon discovered that burns previously treated with tanning agents or triple dyes were certainly composed of an altered substrate. His attempts to employ enzymes on burns along with the use of trypsin by Siler[13] were some of the earliest excursions into enzymatic débridement of burns.

Collagenase prepared from a special strain of *Clostridium histolyticum* (H4) by I. Mandl and J. MacLennan has been studied in my laboratory for 5 years under investigations financed by the Armed Services.[10, 11] A collagenase from another strain has also been isolated by Logan of the Department of Chemistry of the University of Cincinnati[12] and applied clinically to burns by W.

Altemeier of the Department of Surgery.[1] Connell and Rousselot[5] applied some clostridial enzymes to burns. All have found that clostridial enzymes are more successful than other enzymes.

However, fear has always been expressed about using an enzyme produced by an anaerobic bacteria even though the alpha-toxin is removed when it is correctly prepared and the preparation is rendered sterile. Our special strain of histolyticus was selected originally to obtain a nontoxic collagenase. Collagenase attacks all forms, except leatherized collagen, and the character of its attack can be controlled by dilution. Moreover, it fixes rapidly to its substrate so when it is used locally there is little danger of general toxicity. When injected into fresh tissues, it causes hemorrhage at certain concentrations. Interestingly, however, granulations and the site of injury develop resistance to this hemorrhagic producing factor and therefore we have not been troubled with hemorrhage in the treatment of burns. The hemorrhagic factor can be concentrated in the preparation of the enzyme, but we have not found a method as yet to remove it.

Clinically, collagenase at the proper dilution has been used on areas up to 400 square centimeters without a single complication developing that could be attributed to the enzyme. When this enzyme failed, failures have been for the reasons already mentioned. It rapidly takes off the top layers of burned tissue leaving a mat of undigested collagen beneath. This mat is a phenomenon infrequently observed by those treating burns. One does not know whether it is composed of unburned collagen or partially burned collagen nearer to the blood supply and untouched by collagenase. British plastic surgeons who have observed similar mats in burns of the hand have grafted on top of them. We do know that the mat must be removed if granulations are to appear. A stronger concentration of collagenase is still to be tried against it.

Collagenase works well from ointments and with the incorporation of antibiotics.

Collagenase is at present being produced in somewhat larger quantities, and larger clinical trials are being planned for this winter. There are still many problems to be solved in connection with its production and application. Actually the clostridia produce a mixture of enzymes that we have separated by second fractionation. We believe that peptidase and collagenase fractions are the more important constituents and that the peptidase fraction can even be placed below the leatherized burn without causing harm.

Lastly,[7] we have recently shown that the combination of enzyme therapy plus the use of an antibiotic will reduce the bacterial count of infected lesions whereas neither alone will do so. To work, the bacteria must not be resistant and the enzyme must be active. Not all enzymes work. The exact mechanism of action of the enzyme is not clear. We have been able to show also that if one treats an experimental burn on one side of the rabbit with enzyme alone and on the other side with an enzyme plus an antibiotic that although slough separates from both sides at 24 to 36 hours, many bacteria are recovered in quantitative cultures made from the base of the burns treated with enzyme

alone, while there are very few bacteria recovered from the base of the burn treated with the combination. Thus the use of the combination of enzyme plus antibiotic from the time of burning should reduce the possibility of septicemia that may so frequently cause death after extensive burning. Also, this demonstration provides background for the claims that the combination of enzyme plus parenteral antibiotics helps the treatment of abscesses. We achieved sterilization more rapidly when the enzymes were injected about the lesions and recently we have noticed that commercial concerns have been recommending the injection of trypsin and chymotrysin about inflammatory lesions.

REFERENCES

1. Altemeyer, W.: Conference on Enzymatic Débridement of Burns, National Academy of Medicine, October, 1955.
2. Beard, Joseph, Cooper, Gerald, and Hodge, G. B.: Enzymatic Débridement in Local Treatment of Burns, Am. J. Dis. Child. **65:** 909-911, 1943. Also personal communications.
3. Bird, Frank, and Cliffton, E.: Treatment of Acute Abscesses With Human Plasmin, SURGERY **42:** 249, 1957.
4. Cliffton, E, and Connazella, O.: Fibrinolytic and Proteolytic Activity of Human Plasminogen Prepared From Fraction III of Human Plasma, J. Appl. Physiol. **6:** 42, 1953.
5. Connell, J. F., Jr., and Rousselot, L. M.: Further Observations on the Use of Proteolytic Enzymes in the Removal of Burn Eschar, Surg. Forum, Am. Coll. Surgeons **5:** 774, 1955 and personal communications.
6. Connor, Gerard, and Harvey, Samuel: The Pyruvic Acid Method in the Treatment of Deep Clinical Burns, Ann. Surg. **124:** 799-809, 1946.
7. Howes, Edward L.: Reducing the Bacterial Count of the Infected Wound, Lyon Chir. **52:** 199-208, 1956.
8. Howes, Edward L.: Swelling of Catgut Collagen by Acids. Effect on Tryptic Digestion, Presented to Society of University Surgeons, Feb. 14, 1947.
9. Howes, Edward L.: Use of Enzyme in Surgery, S. Clin. North America **36:** 497-505, 1956.
10. MacLennan, John, Mandl, Ines, and Howes, Edward L.: Bacterial Digestion of Collagen, J. Clin. Invest. **32:** 1317-1322, 1953.
11. Mandl, Ines, MacLennan, John D., and Howes, Edward L.: Isolation and Characterization of Proteinase and Collagenase From *Cl. histolyticum*, J. Clin. Invest. **32:** 1323-1329, 1953.
12. Ogle, J. D., and Logan, M. A.: Gelatinase Action of *Clostridium histolyticum*, Fed. Proc. **15:** 523, 1956. Also personal communication with Logan.
13. Siler, V.: Personal communication.
14. Tillet, William.: Studies of Enzymatic Lysis of Fibrin and Inflammatory Exudates by Products of Hemolytic Streptococci, The Harvey Lectures, 1949-50.

Case Reports

RUPTURED ADENOCARCINOMA OF THE APPENDIX

Review of the Literature and Case Presentation

Henry W. Brown, M.D., East Cleveland, Ohio, and Elias A. Husni, M.D., Indianapolis, Ind.

(From the Huron Road Hospital, East Cleveland, and the Cleveland City Hospital)

ADENOCARCINOMA of the appendix is a unique and rare disease. Its pathogenesis and location in such a vulnerable part of the body effect a subtle appearance, almost always behind the mask of appendicitis. McCollum and Pund,[20] in 1951, reported 16 cases of preinvasive carcinoma in appendices removed for reasons other than malignancy. Thus, adenocarcinoma of the appendix lends itself to rather early surgery and probably carries a better prognosis than other malignancies of the intestinal tract.

We have undertaken a review of the literature to date, and only 52 cases could be found which have been proved beyond reasonable doubt to be primary adenocarcinoma of the appendix. Although this disease was described in several papers published prior to 1900, we did not feel justified in including them in this study, because in some there was no histologic study of the tumor and in others no attempt was made to differentiate between adenocarcinoma and the common carcinoid of the appendix.

If, then, we compare this small number of proven cases with the millions of appendectomies performed during the period covered by our review, we can realize the rarity of this condition. The alert surgeon, however, should always consider the possibility of carcinoma whenever the diagnosis of appendicitis is entertained in patients past the age of 40.

The following is a tabulated summary of cases collected from the literature, plus one of our own.

CASE REPORT

D. P., a 64-year-old Negro man, was admitted to the hospital on Sept. 5, 1954, with generalized abdominal pain, nausea, and vomiting of 3 days' duration. The present illness began 2 months prior to this admission, when the patient was brought to the emergency ward with generalized abdominal pain, nausea, and vomiting of 24 hours' duration. A diagnosis of acute appendicitis with rupture was made. An emergency laparotomy disclosed an acute ruptured appendix with generalized purulent peritonitis. The appendix was not removed for technical reasons. Several drains were inserted and heavy antibiotic therapy was instituted. The patient improved steadily and was discharged within 2 weeks. He progressed well until September 2, when he developed generalized abdominal pain, nausea, and vomiting. He was referred to us upon admission on September 5. History and physical

Received for publication Feb. 4, 1956.

TABLE I. CASES OF PROVED PRIMARY ADENOCARCINOMA OF THE APPENDIX

CASE NO.	SEX	AGE	CLINICAL PICTURE OR HISTORY	REMARKS	REF. NO.
1	F	43	Dermoid cyst of ovary	Incidental appendectomy	8
2	M	60	Recurrent right lower quadrant pain	Subacute appendicitis	26
3	F	38	Acute appendicitis	Mucocele with rupture and diffuse pelvic transplantation	26
4	F	49	Pelvic mass		33
5	F	64	Acute appendicitis	Ruptured appendix	27
6	M	36	Acute appendicitis	Ruptured appendix	35
7	F	69	Mass in right lower quadrant		31
8	F	36	Uterine fibroid	Incidental appendectomy	31
9	M	60	Acute appendicitis	Ruptured appendix	31
10	F	50	Gall bladder disease	Cholecystectomy and appendectomy	31
11	M	46	"Stomach trouble" (ulcer)	Gastric resection and appendectomy	31
12	M	40	Acute appendicitis		2
13	F	22	Pelvic pathology	Pelvic surgery and appendectomy	2
14	M	65	Acute appendicitis	Ruptured appendix	2
15	M	48	Ruptured appendix, laparotomy, drainage	Developed mucous fistula	5
16	F	55	Acute appendicitis	Ruptured, with pseudomyxomatous implants of spleen, pelvis, etc.	12
17	F	?	Acute appendicitis		17
18	F	41	Acute appendicitis	Mucocele of appendix	17
19	F	36	Acute appendicitis		17
20	M	51	Mass in right lower quadrant	Abscess of old ruptured appendix	17
21	M	72	Acute appendicitis		21
22	M	57	Acute appendicitis		18
23	M	55	Acute appendicitis		28
24	F	34	Acute appendicitis		28
25	F	40	Mass in right lower quadrant	Appendicoileostomy, with appileocecal intussusception	13
26	M	72	Recurrent right lower quadrant pain	Subacute appendicitis	29
27	M	79	Ruptured appendix	Preoperative diagnosis of ruptured mucocele, carcinoid, or cecal malignancy	9
28	F	19	Recurrent appendicitis	Subacute appendicitis	24
29	M	53	Acute appendicitis		19
30	M	72	Acute appendicitis	Ruptured appendix	15
31	F	58	Mass in right lower quadrant	Abscess of old ruptured appendix	15
32	M	60	Acute appendicitis		15
33	F	43	Acute appendicitis	Ruptured appendix	22
34	F	48	Recurrent right lower quadrant pain	X-ray diagnosis of tumor of appendix	22
35	F	83	Palpable pathology in right lower quadrant	Abscess of appendix with regional enlargement of nodes	22
36	F	54	Palpable mass in right lower quadrant		22
37	F	89	Palpable mass in right lower quadrant		22
38	M	70	Acute appendicitis	Ruptured appendix	3
39	M	53	Acute appendicitis	Ruptured appendix	3
40	M	42	Palpable mass in right lower quadrant	Carcinoma of appendix with metastases to liver, etc.	7
41	F	52	Uterine pathology	Subtotal hysterectomy and incidental appendectomy	23
42	M	56	Acute appendicitis		30
43	M	56	Acute abdomen with palpable mass in right lower quadrant		16

TABLE I—CONT'D

CASE NO.	SEX	AGE	CLINICAL PICTURE OF HISTORY	REMARKS	REF. NO.
44	F	?	Pelvic pathology	Pelvic surgery and incidental appendectomy	32
45	F	26	Acute appendicitis	Peritoneal implants	14
46	M	65	Ruptured appendix	Diffuse carcinomatous transplants in peritoneum 10 months later	10
47	M	39	Acute appendicitis	Ruptured appendix	6
48	M	65	Acute appendicitis		6
49	M	58	Acute appendicitis		6
50	M	?	Palpable mass in right lower quadrant	Needle biopsy diagnoses; laparotomy revealed a large mucous adenocarcinoma filling pelvis	11
51	F	61	Intermittent right lower quadrant pain	Acute appendicitis	1
52	M	71	Acute appendicitis with rupture		1
53	M	64	Acute appendicitis with rupture		Author

examination at this time revealed an irrelevant systemic inquiry, except for a history of arrested tuberculosis of the lungs. The patient was emaciated and had moderate to considerable abdominal distention. There was generalized tenderness of the abdomen, with a questionable mass in the right lower quadrant and increased peristalsis.

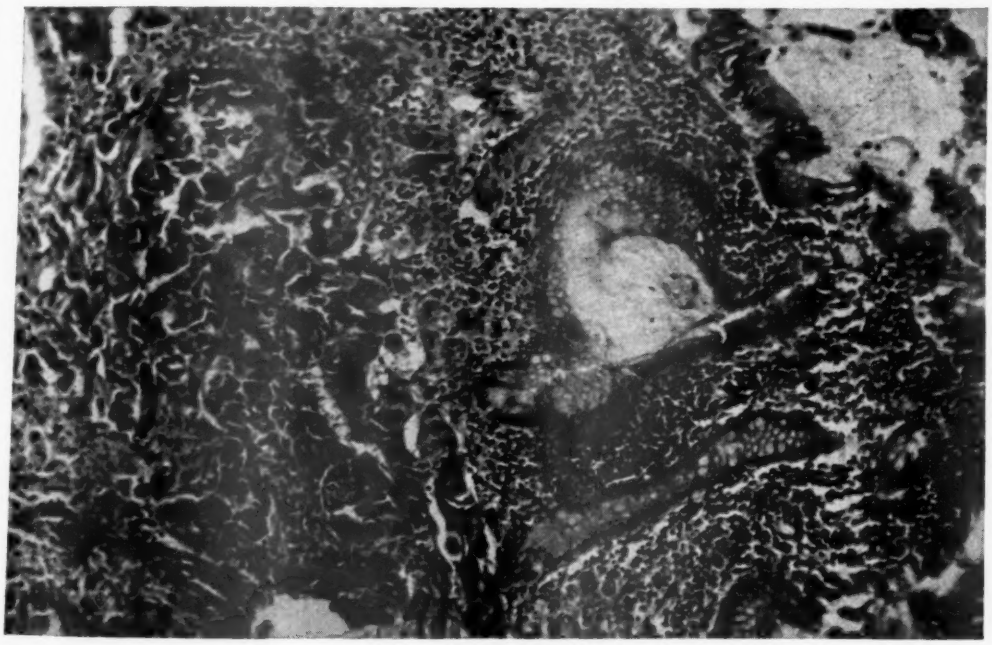


Fig. 1.

Pertinent Laboratory Findings.—Red blood cells, 3,900,000, with hemoglobin of 11.4 Gm. White blood cells, 9,750, with a differential of 73 per cent polycytes and 27 per cent lymphocytes. Blood sugar (fasting), 115 mg. per cent; blood urea nitrogen, 30 mg. per cent; sodium, 130 meq.; potassium, 4.15 meq.; chloride, 88.6 meq. Urinalysis showed a specific gravity of 1.020 with 4 plus albumin. Serology was negative for syphilis.

A scout film of the abdomen revealed a small bowel obstruction in the right lower quadrant, with the possibility of a pelvic abscess. Barium enema studies were noncontributory. A chest film showed evidence of healed or healing miliary tuberculosis. There was a slight pleural effusion of the right side.

The case was diagnosed as possible carcinoma of the cecum. The patient was placed on suction, supportive therapy, and antibiotics. The obstruction persisted. The abdomen was explored on September 17. A tremendous number of adhesions were encountered in the right lower quadrant, causing the small bowel obstruction. These were lysed. The appendix was also removed, showing evidence of old rupture. The pathologist reported primary adenocarcinoma of the appendix with advanced secondary inflammatory changes and abscess formation. In view of the ruptured carcinoma, no further surgery was contemplated. The postoperative course was one of slow progress, and the patient was discharged from the hospital on Oct. 6, 1954.

In studying the cases of primary adenocarcinoma of the appendix described in the literature and our own case, we found that the sex incidence was about even, 28 men to 25 women. Age varied between 22 and 89 years, with an average of 58 years for male patients and 48.26 for female patients. Thirty-two cases presented themselves as acute appendicitis and 3 as subacute. Ten had a palpable right lower quadrant mass, 3 of which were abscesses of old appendicitis with rupture. There were 7 incidental appendectomies. Ruptured appendices totaled 20. Only one was diagnosed by x-ray studies preoperatively. Nine cases had local or distant metastases or implants. There was no follow-up reported on most of the cases. One of the patients who had a ruptured appendix removed returned 10 months later with diffuse peritoneal implants.

The cases presented by McCollum and Pund[20] had an equal sex distribution and varied in age between 17 and 68 years.

DISCUSSION

Adenocarcinoma of the appendix can arise in any part of the organ. It is, however, more common in the proximal half. The incidence of origin of adenocarcinoma in a pre-existing mucocele is an established fact. On the other hand, none of the 17 cases of early carcinoma presented by McCollum and Pund started in a pre-existing polyp. This malignant lesion can probably incite an acute inflammation by one of two ways.

1. Intraluminal growth and obstruction result in distention of the appendix with secretions and so forth. This may exceed the pressure of the vessels in the wall of the appendix, the venous pressure being affected first. Then follows venous obstruction and, depending upon how fast the condition develops, resultant subacute or acute appendicitis with eventual rupture.

2. Infiltration of the appendiceal wall interferes with peristalsis and the emptying of this blind pouch. The same sequence of events follows. The only difference may be that, in the former instance, rupture is usually at the tip of the appendix, whereas here it may occur at the point of infiltration because of the weakened wall.

Preoperative diagnosis in these cases is only speculative. X-ray study occasionally may be helpful in nonacute cases, but this is rare. The ultimate diagnosis rests with the histologic work. Whenever the surgeon suspects the lesion during surgery a frozen section is indicated, for it may save the patient a second trip to the operating room and possibly improve his chances for a cure.

Simple appendectomy may be curative treatment for cases of preinvasive or early adenocarcinoma. If the lesion extends beyond the margin of resection of an acute appendix or if there is invasion of the muscular wall, the established treatment followed in the literature is a right hemicolectomy. Ruptured carcinoma of the appendix, on the other hand, has a poor prognosis because of the implants which attach themselves successfully to the peritoneum. It therefore appears futile to do a radical resection in the face of this complication. As noted above, the incidence of rupture of appendices harboring carcinomatous growth is high. Early surgery may, therefore, be lifesaving.

REFERENCES

1. Burgess, S. B.: Primary Adenocarcinoma of the Appendix; Report of Two Cases, Connecticut M. J. **18**: 501, 1954.
2. Chomet, B.: Carcinoma of the Appendix, Am. J. Clin. Path. **14**: 447, 1944.
3. Clarke, R. G., and Simonds, J. P.: Adenocarcinoma of the Appendix; Report of Two Cases, Am. J. Digest. Dis. **20**: 47, 1953.
4. Costello, C., and Saxton, J.: Appendicitis and Cancer, Postgrad. Med. **9**: 482, 1951.
5. Crile, G., Jr., and Glen, C. G.: Primary Adenocarcinoma of the Appendix; Development of a Mucous Fistula, U.S. Nav. M. Bull. **47**: 328, 1947.
6. Dent, E. D., Jr.: Primary Adenocarcinoma of the Appendix; Report of Three Cases, Mil. Surg. **114**: 191, 1954.
7. Epstein, H. J., Mendell, T. H., and Conston, A. S.: Primary Adenocarcinoma of the Appendix, Am. J. Digest. Dis. **20**: 284, 1953.
8. Frauenthal, M., and Grausman, R. I.: Primary Carcinoma in the Vermiform Appendix; Report of a Case, Am. J. Surg. **19**: 118, 1933.
9. French, W. E., Primary Carcinoma of the Appendix, Am. Surgeon **18**: 313, 1952.
10. Gerber, A., Mackles, A., and Raab, A. P.: Primary Adenocarcinoma of the Appendix; Report of a Case With Ruptured Appendix and Peritoneal Carcinomatosis, New England J. Med. **250**: 505, 1954.
11. Guarino, G. B., and Chitwood, E. M., Jr.: Adenocarcinoma of the Appendix, With a Review of Recent Literature, Am. J. Surg. **87**: 293, 1954.
12. Harryman, J. E.: Mucoid Carcinoma of the Appendix With Pseudomyxoma Peritonei, Harper Hosp. Bull. **5**: 118, 1947.
13. Hughes, J. H.: Adenocarcinoma of the Appendix, Brit. J. Surg. **39**: 282, 1951.
14. Knepper, P. A., Riddell, R. V., and Carpenter, G. T.: Adenocarcinoma of the Appendix, A. M. A. Arch. Surg. **68**: 519, 1954.
15. Lawton, S. E., and Ehrlich, R. W.: Primary Adenocarcinoma of the Appendix, J. A. M. A. **150**: 189, 1952.
16. LeBrun, H. I.: Adenocarcinoma of the Appendix, J. Internat. Coll. Surgeons **20**: 481, 1953.
17. Lee, G. Q., and Blain, J. H.: Adenocarcinoma and Carcinoid of the Appendix, J. Internat. Coll. Surgeons **13**: 197, 1950.
18. Lesnick, G., and Miller, D.: Adenocarcinoma of the Appendix, Cancer **2**: 18, 1949.
19. McCampbell, B. R., and Dickinson, E. H.: Adenocarcinoma of the Appendix, U.S. Armed Forces M. J. **3**: 125, 1952.
20. McCollum, W., and Pund, E. R.: Preinvasive Adenocarcinoma of the Appendix; Report of Sixteen Cases, Cancer **4**: 261, 1951.
21. Marks, E. S., and Whitaker, H. W., Jr.: Primary Adenocarcinoma of the Appendix, SURGERY **27**: 720, 1950.
22. Nardell, S. G.: Adenocarcinoma of the Appendix, Brit. J. Surg. **41**: 136, 1953.
23. Nino, F., Manrique, J., and de All, J. A.: Primary Adenocarcinoma of the Cecal Appendix, Prensa méd. argent. **40**: 1702, 1953.
24. Pezzoli, A.: Adenocarcinoma primitivo del' apéndice cecal, Arch. ital. mal. app. diger. **18**: 1-16, 1952.
25. Rollerston, H. D., and Jones, L.: Primary Malignant Disease of the Vermiform Appendix, Am. J. M. Sc. **131**: 951, 1906.
26. Rosenblatt, M. S., and Robertson, T. D.: Carcinoid and Carcinoma of the Appendix, Northwest Med. **35**: 103, 1936.
27. Schuldt, R. C.: Primary Adenocarcinoma of the Appendix and Carcinoid Tumor, Minnesota Med. **23**: 791, 1940.
28. Sillery, R. J., Primary Adenocarcinoma of the Appendix, J. A. M. A. **147**: 855, 1951.
29. Smith, H. O.: Primary Adenocarcinoma of the Appendix, Canad. M. A. J. **65**: 260, 1951.

30. Tannhauser, S.: Adenoma and Adenocarcinoma of the Appendix, New York J. Med. **53**: 2656, 1953.
31. Uihlein, A., and McDonald, J. R.: Primary Carcinoma of the Appendix Resembling Carcinoma of the Colon, Surg., Gynec. & Obst. **76**: 711, 1943.
32. Vicari, F. A.: Pathology of the Appendix, A. M. A. Arch. Surg. **68**: 329, 1954.
33. Waugh, T. R., and Findley, David: Mucocele With Peritoneal Transplantation in Adenocarcinoma of the Appendix, Am. J. Surg. **37**: 518, 1937.
34. Woolner, L. B.: Carcinoma of the Appendix; Comments on Pathology, Proc. Staff Meet., Mayo Clin. **28**: 17, 1953.
35. Young, E. L., and Wyman, Stanley: Primary Carcinoma of the Appendix Associated With Appendicitis; Report of a Case, New England J. Med. **227**: 703, 1942.

CARCINOMA OF A PARATHYROID GLAND WITH HYPERPARATHYROIDISM

Report of a Case

C. Herbert Fredell, M.D.,* Monroe A. McIver, M.D., and Joseph W. Ferrebee, M.D., Cooperstown, N. Y.

(From the Mary Imogene Bassett Hospital)

INTRODUCTION

CARCINOMA of a parathyroid gland is an infreqent cause of hyperparathyroidism.[1, 7] Cope[3] encountered 4 cases in the course of operative treatment of 148 patients with hyperparathyroidism and in addition reviewed 29 cases reported in the literature which appeared to meet his criteria of malignancy. Black[2] studied 20 reported cases of functioning carcinoma of the parathyroid from the standpoint of treatment and duration of cure or remittance of symptoms.

The following is a case of carcinoma of a parathyroid gland with hyperparathyroidism.

CASE REPORT

P. A. S., a 49-year-old bleaching-machine operator, was first seen at the Mary Imogene Bassett Hospital on Nov. 7, 1954. His complaint was 5 years of bone pain in the back, hips, knees, and ankles, of sufficient severity to force him to discontinue work one year prior to admission. At that time, roentgenograms of the pelvis and femur were thought to suggest Paget's disease and he had received a course of ACTH, cortisone, and phenylbutazone, without improvement. Also at that time, he had complained of right renal colic. Pyelography and cystoscopic examination were said to have revealed no pathology, although he continued to experience occasional costovertebral angle pain. Mild postprandial epigastric distress was relieved by alkalis. The basal metabolic rate was reported as elevated and the patient complained of nervousness, palpitation, and bouts of anxiety. In October, 1954, his condition deteriorated. There were vertigo, weakness, and unsteadiness of gait, two episodes of syncope, and the onset of pain in the rib cage on the left aggravated by respiration.

Physical examination revealed a thin, short, white man who appeared older than his stated age. His gait was unsteady and he complained of pain on motion of his back and legs. There was tenderness over the eighth through eleventh ribs on the left. Muscles were wasted. There was a gross tremor of the fingers, and a clubbing of the finger tips with shortening of the terminal phalanges, particularly of the right index finger. Calcified conjunctival concretions were present and examination of the neck revealed a mass 3 cm. in diameter on the right side, in the area of the lower pole of the thyroid. This mass moved on swallowing and was not tender. No lymhadenopathy was detected. X-ray examination of the skeleton showed generalized osteoporosis with many areas of cyst formation particularly obvious in the ribs. The distal phalanges showed destruction, with collapse of the soft tissue about them. Calcification was present in the aorta, and a diffuse

Received for publication March 2, 1956.

*Present address: 121 East Aspen Avenue, Flagstaff, Ariz.

mottled calcification was present in the kidneys, with poor renal function as seen by intravenous pyelography. Calcification was present in the center of the tumor mass on the right side of the neck. This mass encroached upon the esophagus, but lay outside it, and the mucous membrane over it was intact.

The blood count was normal. Blood urea nitrogen was 22 mg. per cent, serum calcium 7.6 meq. per liter, serum phosphorus 4.8 mg. per cent, alkaline phosphatase 39.5 King units. Urinalysis revealed a specific gravity of 1.012, one plus albuminuria, urine Sulkowitch test one plus, and 9.5 meq. of calcium per liter of urine. Phenolsulfonphthalein excretion was 15 per cent in 2 hours. The basal metabolic rate was plus 21.

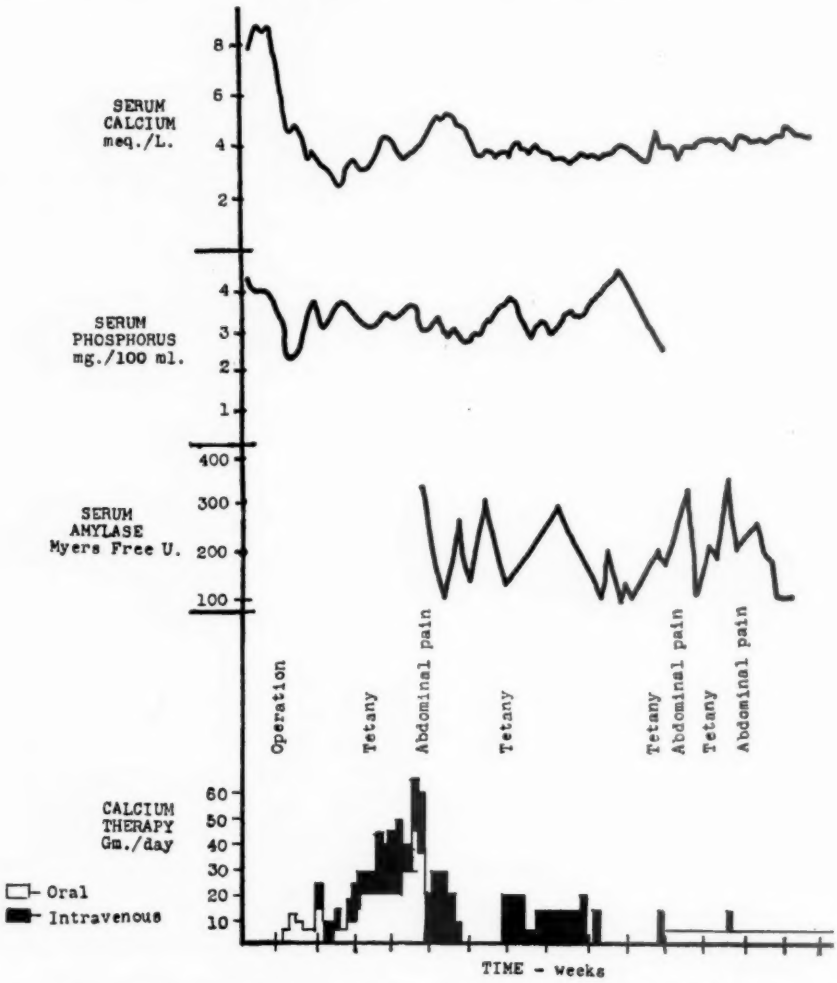


Fig. 1.—The serum levels of calcium, phosphorus, and amylase are shown. The serum calcium fell markedly the day following the removal of the parathyroid carcinoma. There was the usual correlation between postoperative tetany and low serum calcium. The episodes of abdominal pain, diagnosed as acute pancreatitis, were accompanied by a rise in serum amylase. The postoperative calcium therapy is shown in relation to the clinical course and serum calcium values. (The calcium therapy was calcium lactate orally and calcium gluconate intravenously.)

Operation on Nov. 16, 1954, revealed a tumor that was densely adherent to the trachea, esophagus, and right lobe of the thyroid and involved the recurrent laryngeal nerve. The tumor was separated from the trachea and esophagus by sharp dissection; the recurrent laryngeal nerve on the right was sacrificed and the right lobe of the thyroid removed. No abnormal lymph nodes or other tumor masses were encountered.

Fig. 2.—The barium esophageal swallow shows displacement of the esophagus by a partially calcified tumor. The area of calcification of the tumor is slightly below the point of maximal displacement.

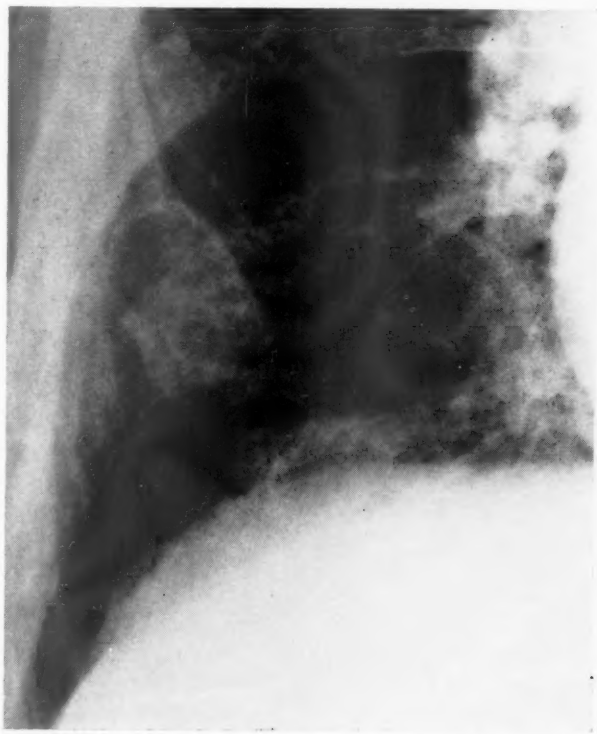


Fig. 3.—A closeup of a cystic area in a rib on the right and generalized decalcification of the ribs is shown.

The pathologist, Dr. C. V. Z. Hawn, reported that the tumor measured 4 by 3 by 1 cm., was irregular and hard, and contained several spherical calcified areas within it. Microscopically, there was a fibrous capsule with numerous trabeculae coursing throughout and separating nests and large sheets of cells identified as parathyroid in origin. In some areas there was marked pleomorphism with frequent mitotic figures and areas of anaplasia. Other areas showed mucoid degeneration, hyalinization, and calcification. At the periphery, invasion of the blood vessels occurred and in some areas there was perineural invasion of the nerves. Dr. Benjamin Castleman reviewed the microscopic sections and concurred in the diagnosis of adenocarcinoma of the parathyroid gland.

Fig. 4.—Decalcified areas of the distal phalanges which accompany the clubbing of the fingers.

During the first 2 postoperative days the patient's blood pressure was low, the urinary output poor, and the blood urea nitrogen rose to 55 mg. per cent. With improvement in blood pressure, urinary output and blood urea nitrogen returned to normal. As illustrated in Fig. 1, the serum calcium and serum phosphorus concentration showed the changes to be expected following removal of a functioning tumor of a parathyroid gland. Calcim gluconate by mouth and by vein in the amounts indicated and a diet low in phosphorus failed to prevent the development of frank tetany on the fourteenth postoperative day. Increase in the constant administration of calcium, by intravenous route, appeared to control the tetany but was associated with the appearance of red tender areas involving the left ankle and mandibular region. An episode of acute abdominal pain, with serum amylase of 350 Myers Free Units, occurred on December 10 and was diagnosed as acute pancreatitis. The pain, nausea, and vomiting subsided under treatment with atropine, but vague epigastric distress with periodic vomiting persisted for many days. Similarly, episodes of mild and

at times quite severe tetany occurred periodically, as recorded in Fig. 1. Eventual stabilization of serum calcium and serum phosphorus concentrations at levels approximating normal was obtained by the administration of dihydrotachysterol, 1.25 mg. a day by mouth, 5 Gm. of calcium gluconate, and a bland sippy diet of 6 feedings. On this regime the abdominal distress also disappeared and the patient was discharged on the ninety-fifth postoperative day.

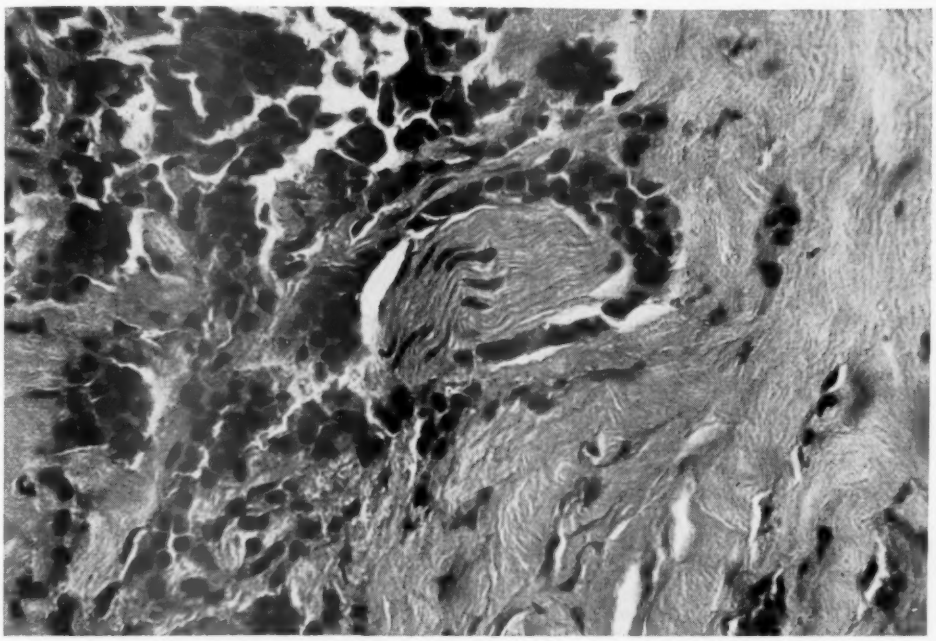


Fig. 5.—Photomicrograph showing the perineural invasion by tumor cells, one of the criteria of malignancy.

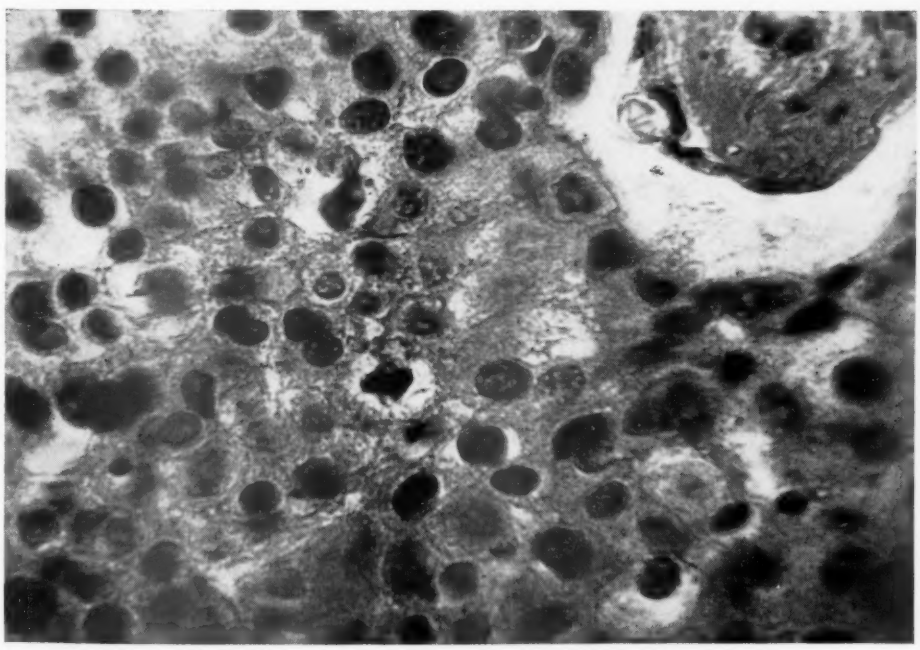


Fig. 6.—Photomicrograph showing mitoses.

After discharge from the hospital, follow-up examination and report at 3, 6, and 9 months revealed that he had gained strength and weight steadily. Vitamin D in doses of 50,000 units twice a week had been substituted for the dihydrotachysterol; he had liberalized his diet, and he was essentially asymptomatic. However, he continues to have a hypertension of 170/100, a urinary specific gravity of 1.009, and a negative Sulkowitch's test. Despite albuminuria of four plus, his blood urea nitrogen remains normal, and his serum calcium and phosphorus levels are within normal limits.

DISCUSSION

This patient had hyperparathyroidism with bone disease and secondary renal involvement. The preoperative diagnosis of functioning parathyroid carcinoma as a cause of the hyperparathyroidism was considered chiefly on the observation that the carcinoma usually is palpable, while the adenoma is not.[2] The operative finding of intense fibrous, inflammatory reaction surrounding the tumor and binding it to the adjacent structures was characteristic.[3, 6] In this particular case, a radical dissection of the cervical lymphatics was not done because no enlarged lymph nodes were detected and local invasion of the trachea, and perhaps of the esophagus, was suspected. Roentgen ray therapy was given in the amount of 7,700 r. during the first postoperative month.

Black[2] has discussed the prognosis that may be expected in carcinoma of the parathyroid gland. He found that over one-half of the patients had had metastases before the time of surgery. Of 8 cases that appeared to be locally invasive, only 6 had been treated by radical surgery, including radical neck dissection; 3 of these were well for an average of 40 months postoperatively, and 3 others had recurrence an average of 19 months later. The average total course of the disease in those patients who had succumbed was an average of 69½ months.

In the case here reported the complicating factor of renal calcinosis and insufficiency appears nonprogressive, now that the hypercalcemia has been corrected, though such is not always true.[4, 5] Careful postoperative follow-up studies were made in order to maintain a positive calcium balance without reintroducing a period of hypercalcinuria. It is important in this regard that the patient was instructed to have Sulkowitch tests on his urine and to adjust his calcium intake accordingly.

The episodes of acute pancreatitis that occurred during the early postoperative period presented a major difficulty in the patient's convalescence, interfering as they did with proper nutrition and proper maintenance of calcium intake. It is interesting that pancreatitis has occurred in other patients with carcinoma of the parathyroid.[2, 3] This patient is the fourth individual in a series of 34 cases, who has suffered from this complication.[7] This is an incidence that seems a little high for pure coincidence. Its mechanism is not known, but it is tempting to speculate upon the possibility that it may be associated with an inflammatory reaction surrounding areas of metastatic calcification even though in this instance no such areas could be detected by

x-ray. It is noteworthy that both the pancreatitis and the episodes of inflammatory reactions around the left ankle region, thigh, and mandible were associated with the rather considerable intravenous administration of calcium salts that was required to control the tetany.

SUMMARY

A report is given of a patient with a carcinoma of a parathyroid gland, hyperparathyroidism with bone disease, and renal calcinosis with renal insufficiency. The postoperative course was characterized by tetany and episodes of acute pancreatitis. The clinical features, complications, operative treatment, pathology, and prognosis of carcinoma of the parathyroid gland with hyperparathyroidism are briefly reviewed.

REFERENCES

1. Albright, F., and Reifenstein, E. C. J.: The Parathyroid Gland and Metabolic Bone Disease: Selected Studies, Baltimore, 1948, Williams & Wilkins Company.
2. Black, B. K.: Carcinoma of the Parathyroid, Ann. Surg. **139**: 355-363, 1954.
3. Cope, O., Nardi, G. I., and Castleman, B.: Carcinoma of the Parathyroid Glands; 4 Cases Among 148 Patients With Hyperparathyroidism, Ann. Surg. **138**: 661-671, 1953.
4. Goldman, L.: Unusual Manifestations of Hyperparathyroidism, Surg., Gynec. & Obst. **100**: 676-689, 1955.
5. Hellstrom, J.: Clinical Experience of 21 Cases of Hyperparathyroidism With Special Reference to the Prognosis Following Parathyroidectomy, Acta chir. scandinav. **100**: 391-421, 1950.
6. Norris, E. H.: Collective Review; Carcinoma of the Parathyroid Glands With Preliminary Report of 3 Cases, Internat. Abstr. Surg. **86**: 1-21, 1948.
7. Stephenson, H. U., Jr.: Maligant Tumors of the Parathyroid Glands; Review of Literature with Report of a Case, Arch. Surg. **60**: 247-266, 1950.

Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

DR. CONRAD RAMSTEDT AND PYLOROMYOTOMY

WILLIAM F. POLLOCK, M.D., AND WILLIAM J. NORRIS, M.D., LOS ANGELES, CALIF.

(*From the Department of Surgery, University of California at Los Angeles School of Medicine*)

THE operation of pyloromyotomy for the treatment of pyloric stenosis stands exalted in the armamentarium of the general surgeon as the most consistently successful operation ever described. The history of its discovery hinges on the work of a man who has recently celebrated his ninetieth birthday in the German city where he first described this triumph—Dr. Conrad Ramstedt of Munster, Westphalia.

In preparing a recent report of 1,422 cases of pyloric stenosis operated upon at the Los Angeles Children's Hospital during the period from 1934 through 1955, we undertook a detailed survey of the literature, including the translation of the original articles in the German literature. We encountered the same little features in the development of the story that have puzzled and intrigued two generations of surgeons since the publication of the original description in 1912.

Many students of this disorder have noted the fact that in the original description of the operative technique in the *Medizinische Klinik* of 1912 the name of the author was Conrad "Rammstedt." In his subsequent reports dating from 1930 his name was consistently spelled "Ramstedt." There has also been the persistent account that the operation was devised on the spot with the abdomen open because the pressure of the situation prevented the completion of the originally planned Weber (or Fredét) operation of transverse suture of the cut edges of the pyloric muscle.

A short note in a recent surgical journal noting the fact that Dr. Ramstedt had recently celebrated his ninetieth birthday was called to our attention by Dr. C. J. Berne, Professor of Surgery at the University of Southern California School of Medicine, and a correspondence was immediately begun with Dr. Ramstedt.

The translations of his communications in German have been proofread and edited in part by Mrs. Ellen Work, by Dr. Norbert Werk, and by Dr. Ramstedt's daughter, Eva, who is now living in Los Angeles and working at the California Hospital.

Received for publication Aug. 22, 1957.

Dr. Ramstedt wrote that the explanation for the change in spelling of his name is derived from the fact that in Germany prior to World War I it was the common practice for the family records to be a part of the church records for certain occasions, such as birth, marriages, and so forth. Prior to World War I he had spelled his name "Rammstedt." During and immediately after the war he undertook an inquiry into his own genealogy. He was surprised to discover that his grandfather had apparently made an error in the entries in the church records of the family and that prior to the entries by his grandfather the name had been spelled "Ramstedt." In 1920 Dr. Conrad Ramstedt accordingly changed the spelling of his name to conform to the earlier records and he has consistently used the spelling with one *m* since that time. An earlier letter indicates that he considers this the correct spelling and his daughter uses this spelling, also. His son, who is an engineer living in Germany, still uses the form with two *m*'s.

The question of the original development of the operation is partially answered by a careful perusal of his original article in which he described in detail what he did. His reflections on this case 46 years later are extremely interesting and it seems best to let him report the case in his own words. The following is a partial translation of a letter from him, dated July 30, 1957, in reply to a request for his thoughts on this case and the eventual wide acceptance of the operation.

> In August, 1911, the pediatrician, Dr. Schulte, who was chief physician of the Children's Hospital in Munster, approached me to undertake an operative attack on a case of congenital pyloric stenosis that was showing no improvement in spite of every medical treatment. I was moderately surprised and somewhat under pressure, first, because I had never before seen a case of this disease which is so dangerous in newborns and second, because it was the first-born son of an especially famous count's family in Westphalia.
>
> To be sure, this disease was moderately familiar to me from the literature, but it had been considered only rarely by surgeons before that time and the pediatricians had only recommended an operation as a last resort. I reviewed the operative methods which could be used. Resection of the pylorus, gastroenterostomy, and stretching of the narrowed pylorus after the method of Loreta seemed to me from the beginning to be too aggressive for an infant, although they had been attended by success in certain isolated cases. One would have to devise an operative attack which could be done with the simplest and most expeditious opening of an abdominal incision in such a small person. These considerations seemed to me to be best fulfilled by the extramucosal pyloroplasty which Payr and Mikulicz had used in adults, which Fredét in Paris in 1908 had used for the first time in infants with pyloric stenosis successfully in isolated cases, and which Weber in Dresden in 1910 had used in 3 infants with one death. Although success could not be completely assured with this operative procedure, it still seemed to me to be the best, since with this method the stomach and duodenum would not be opened and infection from the stomach contents was virtually excluded. I decided therefore to undertake this operative procedure in the tiny patient.

At the laparotomy on Aug. 23, 1911, I was astonished at the pyloric tumor as thick as my thumb. After I had split the tumor down to the mucosa for a distance of about 2 cm. I had the impression that the stenosis had been relieved. I still tried, however, to accomplish the previously described plastic procedure by transverse suture of the muscle edges. However, the tension on the sutures was so very strong that the first one cut through immediately. Then the thought shot through my head, "A plastic alteration of the cut edges is completely unnecessary; the stenosis seems to be already relieved by a simple splitting of the pyloric muscle and coincidentally the spasm as well, which is the characteristic basis of the disease." I did not complete the plastic operation on the muscle which had been originally planned but left the cut gaping, covering it with a tab of omentum for safety's sake and ended the operation. The little one vomited a few times for the first few days which I attributed to the sutures placed at the beginning, but he recovered promptly and completely to the great joy of his parents.

I proposed to undertake only a simple splitting of the pyloric muscle if I should ever have occasion to operate upon a second case. If the cause of this disease is a spasm, this should be able to do away with it and with the stenosis in a single blow.

It was not until a year later, however, on June 18, 1912, that I had an opportunity to follow my plan and operated upon a male infant who had already become very depleted, but this was similarly done with complete success. This was all the more impressive to the parents since they had already lost 2 sons from pyloric stenosis and a daughter had had to have medical treatment for 5 months before she finally recovered.

In September, 1912, I reported these 2 cases to the Natural Science Assembly at Munster and recommended the simple splitting of the pyloric muscle (pyloromyotomy) in cases of pyloric stenosis which were resistant to expectant treatment.

It was not until many years later, however, that pyloromyotomy found recognition and wider dissemination. Perhaps the war was to blame for this, since the doctors of the whole world had other much greater problems. Perhaps the disease was seldom observed because of the decline in the birth rate from 1914 to 1919. But more likely it was the well-justified distrust of the pediatricians since the operative methods previously employed seemed to be of dubious value when compared to the improvements made with medical treatment from year to year. During the war some confirmatory communications appeared by Wilms, Drachter, Gulecke, and Monnier.

After the war Kirchner in 1922 published (through his pupil Hein) a report of 4 cured cases treated by pyloromyotomy and took the occasion to recommend early operation in every way he could. In that same year Heile and I reported even greater numbers, notably 20 cases with only 1 death, and I reported 17 consecutive cured cases without a death.

In spite of this, when I gave a speech at the Association of Pediatricians of the Rhineland and Westphalia in Munster in 1925, I received some definite objections from the chairman, the renowned pediatrician Professor Schlossmann of Dusseldorf. It surely would have been disseminated even more widely in time, but it first achieved resolute significance when Kirschner of Tubingen at the 1928 Surgical Congress entered energetically into an evaluation of the pros and

cons of the earlier operations for pyloric stenosis and then supported this one with a consecutive series of 22 infants cured by pyloromyotomy without mortality. After that the whole question of the operative treatment of pyloric stenosis was placed in the foreground and many pediatricians altered their former completely antagonistic viewpoint, in particular the previously named Professor Schlossmann who had been using medical treatment almost exclusively for these infants.

I had the great joy and satisfaction of having him inform me of this in a letter in which he concluded with remarkable candor, "I have changed from Saul to Paul." In the meantime the Ramstedt operation had long been recognized elsewhere, especially in the United States of America, since numerous communications came to me from there.

I have operated upon about 70 infants myself and I must lamentably note 2 deaths in infants who were too weak to withstand the operation. Aside from the first 2 patients operated upon in the years 1911 and 1912, 2 young girls stand out especially in my memory. One had been on medical treatment for 6 months before I saw her, had shown some temporary improvement, but vomited again and again, and was in an obviously grievous condition. From the history and physical findings it had to be a case of a hidden pyloric. Laparotomy confirmed this presumption. I split the markedly thickened pylorus in the usual way. The child recovered rapidly and completely, and this little one is today a happy mother with several children.

In the second case I had done a typical pyloromyotomy on Aug. 7, 1930. Although the wound healed promptly the vomiting persisted. With medical treatment the little one was barely kept alive. By September 5, Dr. Schulte, the pediatrician, urged that another operation be done, particularly after the x-ray examination had demonstrated a complete stenosis of the pylorus. At operation on September 6, the first cut in the thickened pylorus was completely healed. I made a second cut just over the first but down to the mucosa. The little one stopped vomiting at once. Why the first operation was unsuccessful is not clear to me. This case has been described by me in *Chirurg.* (**3**: 449-451, 1931).

Dr. Ramstedt's article in 1931 was entitled "Is Pyloromyotomy the Treatment of Choice for Pyloric Stenosis?" and his conclusion was essentially the same as our own would be today; it is. The remarkable results that can be obtained with this operation have been reported many times from many centers. There can be no doubt that most of the improvement in recent years has come from better understanding and control of the fluid and electrolyte problems of these patients. The preparation of these infants for the surgical relief is an excellent example of practical pediatric therapy, and their anesthetic management has likewise shown remarkable advances.

The first case was operated upon by Dr. Ramstedt on Aug. 23, 1911, but was not discharged from the hospital until the following January. Both of his first 2 cases developed diarrhea postoperatively which was treated with opium and dietary changes.

Those who have read Ram(m)stedt's original article will recall his statement about the technical skill required to do a gastroenterostomy in an infant whose "whole body shuddered with the effort of its labored breathing" and the

"markedly depleted state" of the infants from the incessant vomiting. The fatal infections which resulted from opening the mucosa was the principal reason the various extramucosal procedures described earlier by Fredét (1908) and by Weber (1910) had been developed. Happily, these problems have all been solved for us and we can now operate upon a well-hydrated, physiologically stable baby with a quiet operative field and a negligible risk of serious infection—all the more credit to men able to achieve a good cure rate without these benefits.

Book Reviews

CONDUCTED BY J. GARROTT ALLEN, M.D.

Synopsis of Gastroenterology. Rudolph Schindler. New York, 1957, Grune & Stratton, Inc. $7.75.

The author has designed *Synopsis of Gastroenterology* as a ready reference for the general practitioner and the internist. The material is presented in text form without illustrations. The gastrointestinal tract, from the oral cavity to the rectum and including the accessory organs, is discussed. First every symptom and then every disease in gastroenterology is discussed and each is a complete unit in itself. Necessarily, however, this leads to moderate repetitions in the book as a whole, especially in the listing of nonspecific symptomatology. In a quest for thoroughness, discussions of now rare diseases, such as syphilis and tuberculosis of the gastrointestinal tract, are included.

For simplicity and brevity, the author has omitted all documentations, and many of the concepts of disease developed in the book are his own. Many suggestions in management reflect the author's clinical training in prewar Germany.

The asset of being a ready, concise, clinical reference book is invariably associated with the debit of being relatively lacking in the discussion of the fascinating physiologic theories which are the basis of modern medical and surgical therapy.

The meticulously thorough listings of the table of contents and general index make it an exceedingly convenient book to use.

—Herzl Ragins

Local Anesthesia and Pain Control in Dental Practice. Leonard M. Monheim. St. Louis, 1957, The C. V. Mosby Company. Pp. 299, 128 ills. $8.75.

This rather comprehensive volume on regional anesthesia in the oral cavity is Dr. Monheim's first book in the field. However, it is based on countless lectures he has presented to his many students in the Pittsburgh area. The author is also one of those unique individuals (following the precedent set by Wells and Morton a century ago) who came into the realm of anesthesiology by way of dentistry.

It is rare to have a textbook devoted entirely to local anesthesia in the oral area. While this volume touches upon general anesthetic agents and methods of sterilization, by and large, it is a good compendium on anesthesiology concerned with the locale of the mouth. The text is replete with illustrations (128 figures), both photographic and diagrammatic, all of which help the reader to visualize the three-dimensional phenomenon of inducing local anesthesia by way of depositing the appropriate anesthetic agent at the proper intra- and extraoral site.

The chapter on injection techniques presents clearly and concisely in outline form the procedures employed in securing regional analgesia in the dental and oral area. Extraoral injection techniques for this area are described in considerable detail, in addition to the usual intraoral methods.

There are supplementary chapters on medicolegal aspects of anesthesia and on descriptive anatomy of the trigeminal nerve and other nerves supplying the facial region. A valuable chapter has been reserved for anesthetic complications including office emergencies and their treatment.

Other chapters in the book deal with the pharmacology and chemistry of local anesthetic solutions, vasoconstrictors, specific drugs used for preanesthetic medication, and those prescribed for controlling postoperative pain.

The armamentarium for local anesthesia is discussed thoroughly, including the aspirating type syringes and the aspirating type carpules.

The author clearly defines anesthetic terms and meticulously differentiates between words often used interchangeably by members of the profession. There is a strict adherence to accurate and correct nomenclature throughout the text. A useful glossary of pertinent words appears at the end of the book. Formulas and generic terms of anesthetic agents are well portrayed in Chapter Five. This kind of explanation would be essential for the novice in order to avoid confusion with the vast number of proprietary terms used in the anesthetic field.

This volume, in finality, exemplifies the author's firm belief that "pain and dentistry should not be synonomous" and certainly emphasizes that there is no excuse for pain in dental practice today when local anesthesia is at the disposal of every competent practitioner.

—Frank J. Orland

Congenital Anomalies of the Viscera. Their Embryological Basis. J. L. Bremer. Cambridge, Mass., 1957, Harvard University Press. $5.00.

The term "congenital anomaly" is often lightly employed by a significant number of physicians for the occasional bizarre condition they may encounter. Unfortunately, such a designation frequently represents the greatest extent of their understanding of the problem with which they are confronted. In his book, *Congenital Anomalies of the Viscera*, the author has "at least in part" supplied a succinct source material which should greatly aid in rectifying this situation.

As indicated by the title, this work deals solely with anomalies of the viscera and involves other areas only insofar as they relate to the primary topic. In general, each section begins with a review of the embryologic development of the organ or organ system. This is then followed by a discussion of the genesis of the various anomalous formations peculiar to that organ by virtue of deviations in its developmental anatomy. In areas of controversy, such as the character and formation of the alveolar wall and the mechanism of production of transposition of the great vessels, evidence is presented for all points of view and is followed by the author's own concept.

In addition to a textbook of histology, Dr. Bremer, Professor of Anatomy, Emeritus, at Harvard University, has, over many years, contributed much in the way of original investigation to this field. It is perhaps because of this that his style of writing is engaging and almost conversational. The text is abundantly illustrated by simple diagrams as well as a few drawings and photographs.

In 196 pages, Dr. Bremer has provided interesting and instructive reading which should appeal not only to pediatricians but also to surgeons and internists.

—Robert S. Levine

Spinal Cord Compression. I. M. Tarlov. Springfield, Ill., 1957, Charles C Thomas. Pp. 130. $7.50.

In this short book of 130 pages, Dr. Tarlov presents his studies of compression of the mammalian spinal cord and, in the light of this knowledge and of clinical experience, outlines the management and indicates the prognosis of those cases of spinal cord compression encountered in clinical practice. He has found in dogs that acute compression of a severity somewhat short of that causing disruption of the cord must be relieved in a very few minutes if recovery will follow. In acute compression by a force just sufficient to cause paralysis of conduction, the period of tolerance is about 3 hours. If the pressure is applied gradually over 48 hours, then recovery may be expected if decompressed within a week. If some spinal cord function remains, recovery may be expected after several weeks' compression.

Turning to the clinical end of the study, it is usually impossible in acute trauma to afford decompression within a matter of minutes or even 3 hours. Nevertheless, a few cases of minimal compression must exist and there is a sufficient number of well-documented cases of postoperative recovery after approximately 24 hours' paralysis to justify the procedure in all cases of complete paraplegia with manometric block. In the cases of slow compression, such as that caused by benign intradural tumors, if decompression is atraumatic and the removal is complete, recovery may be expected even after months of paralysis. Where any conduction remains (and pain is the last to persist) the prognosis is correspondingly better. These clinical conclusions are those accepted by the majority of neurosurgeons. Dr. Tarlov has provided experimental confirmation of their validity. In addition, further theoretical considerations such as the role of direct pressure and that of compression anoxia, the importance of the site of compression and the part cleared by the dentate ligaments are also discussed. For those becoming acquainted with the problems of spinal cord compression, this book will provide much useful information.

—John F. Mullan

ANNOUNCEMENT

Seventh International Cancer Congress, London

Those planning to attend the Seventh International Cancer Congress, which will take place at the Royal Festival Hall, London, July 6-12, 1958, are reminded that enrollment forms must be received at the Congress Office (45 Lincoln's Inn Fields, London, W. C. 2) by Jan. 1, 1958, if a late fee is not to be incurred. Registration forms may be obtained from the Secretary-General at that address.

Calendar of Surgical Meetings

1957

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 11-13, 1957, The Cloister, Sea Island, Ga. Deadline for papers, Aug. 15, 1957. Secretary, Dr. Eben Alexander, Jr., Bowman Gray School of Medicine, Winston-Salem, N. C. Attendance at meetings by invitation only.

AMERICAN MEDICAL ASSOCIATION. *Clinical Meeting,* Dec. 3-6, 1957, Auditorium, Philadelphia, Pa. Deadline for papers, July 15, 1957. Secretary, American Medical Association, George F. Lull, M.D.; Secretary, Council on Scientific Assembly, Thomas G. Hull, M.D.; address of both, 535 North Dearborn Street, Chicago 10, Ill.

PAN-PACIFIC SURGICAL ASSOCIATION. *Seventh Congress,* Nov. 14-22, 1957. Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 10-12, 1957, Greenbrier Hotel, White Sulphur Springs, W. Va. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore 18, Md. Guests are invited by the Secretary at the request of the Membership.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 21-23, 1957, Hotel Utah, Salt Lake City, Utah. Deadline for submission of papers, Aug. 15, 1957. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.

1958

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* April 23-25, 1958, Edgewater Gulf Hotel, Edgewater Park, Miss. Secretary-Treasurer, Dr. Wm. J. Engel, 2020 East 93rd Street, Cleveland, Ohio.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 16-18, 1958, Statler Hotel, Boston, Mass. Secretary, Dr. H. T. Langston, 1919 West Taylor Street, Chicago 12, Ill.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 19-21, 1958, The Grove Park, Asheville, N. C. Secretary, Dr. Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* April 16-18, 1958, Waldorf-Astoria, New York, N. Y. Secretary, Dr. William A. Altemeier, Cincinnati General Hospital, Cincinnati, Ohio.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* April 28–May 1, 1958, Roosevelt Hotel, New Orleans, La. Deadline for submission of papers Dec. 1, 1957. Secretary, Dr. Samuel L. Raines, 188 South Bellevue Boulevard, Memphis 4, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 20-22, 1958, Columbus, Ohio. Deadline for submission of abstracts, Nov. 15, 1957. Secretary, Dr. Charles D. Branch, 1002 N. North Street, Peoria, Ill.

THE HARVEY CUSHING SOCIETY. *Annual Meeting,* April 21-23, 1958, The Mayflower, Washington, D. C. Secretary, Dr. David L. Reeves, 316 West Junipero Street, Santa Barbara, Calif.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Papers, dealing with new and unpublished work, must be submitted with abstract (not over 200 words) before October, 1957. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 3-5, 1958, Biltmore, Santa Barbara, Calif. Secretary, Dr. Carlton Mathewson, Stanford University Hospital, San Francisco, Calif.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 13-15, 1958, Boston, Mass. Deadline for submission of abstracts three months prior to meeting. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.